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(54) Title: ARYL-SULFONAMIDE DERIVATIVES FOR USE AS CCR3 ANTAGONISTS IN THE TREATMENT OF INFLAMMATORY AND IMMUNOLOGICAL DISORDERS

(57) Abstract: The present invention relates to a sulfonamide derivative which is useful as an active ingredient of pharmaceutical preparations. The sulfonamide derivatives of the present invention have CCR3 (CC type chemokine receptor) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with CCR3 activity, in particular for the treatment of asthma, atopic dermatitis, allergic rhinitis and other inflammatory/immunological disorders.



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ARYLSULFONAMIDE DERIVATIVES FOR USE AS CCR3 ANTAGONISTS IN THE TREATMENT OF
INFLAMMATORY AND IMMUNOLOGICAL DISORDERSSULFONAMIDE DERIVATIVES

TECHNICAL FIELD

5 The present invention relates to a sulfonamide derivative which is useful as an active ingredient of pharmaceutical preparations. The sulfonamide derivatives of the present invention have CCR3 (CC type chemokine receptor 3) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with CCR3 activity, in particular for the treatment of asthma, atopic dermatitis, allergic rhinitis
10 and other inflammatory/immunological disorders.

BACKGROUND ART

15 Chemokines are chemotactic cytokines of which major functions are migration of inflammatory cells that express relevant chemokine receptors on their surfaces to sites of inflammation, and activation of inflammatory cells. There are two classes of chemokines, C--X--C (.alpha.) and C--C (i), depending on whether the first two cysteines are separated by a single amino acid (C--X--C) or are adjacent (C--C).

20 One of the C-C family of chemokines, eotaxin, is an 8.4 kDa (74 amino acid) polypeptide and binds with high affinity solely to the receptor CCR3. *In vitro* and *in vivo* eotaxin causes chemotaxis of inflammatory cells expressing CCR3 [Elsner J., Hochstetter R., Kimming D. and Kapp A.: Human eotaxin represents a potent activator of the respiratory burst of human eosinophils. Eur. J. Immunol., 26: 1919-
25 1925, 1996.].

The chemokine receptor CCR3 is a G protein-coupled, seven transmembrane domain receptor (GPCR) which binds to known ligands, in addition to eotaxin, including eotaxin-2 (CCL24), RANTES (CCL5), MCP-3 (CCL7) and MCP-4 (CCL13). CCR3
30 is expressed on inflammatory cells relevant to the chronic asthma pathology. Such inflammatory cells include Eosinophils [Sabroe I., Conroy D.M., Gerard N.P., Li Y.,

Collins P.D., Post T.W., Jose P.J., Williams T.J., Gerard C.J., Ponath P.D. J. Immunol. **161**: 6139-6147, 1998], basophils [Uguccioni M., Mackay C.R., Ochensberger B., Loetscher P., Rhee S., LaRosa G.J., Rao P., Ponath P.D., Baggiolini M., Dahinden C.A. J. Clin. Invest. **100**: 1137-1143, 1997], Th2 cells [Sallusto F., Mackay C.R., Lanzavecchia A. Science. **277**: 2005-2007, 1997], alveolar macrophages [Park I.W., Koziel H., Hatch W., Li X., Du B., Groopman J.E. Am. J. Respir. Cell Mol. Biol. **20**:864-71, 1999] and mast cells [Oliveira S.H. and Lukacs N.W. Inflamm. Res. **50**: 168-174. 2001]. Very recently, it was reported that BEAS-2B, an epithelial cell line, stimulated with TNF- α and IFN- γ , expressed CCR3 [Stellato C., Brummet M.E., Plitt J.R., Shahabuddin S., Baroody F.M., Liu M., Ponath P.D., and Beck L.A. J. Immunol., **166**: 1457-1461, 2001.].

In animal models, eotaxin-knockout mice showed decreased eosinophilia after antigen challenge [Rothenberg M.E., MacLean J.A., Pearlman E., Luster A.D. and Leder P. J. Exp. Med., **185**: 785-790, 1997] and in IL5-/eotaxin- double knock-out mice there is no eosinophilia or AHR in response to antigen challenge [Foster P.S., Mould A.W., Yang M., Mackenzie J., Mattes J., Hogan S.P., Mahalingam S., McKenzie A.N.J., Rothenberg M.E., Young I.G., Matthaei K.I. and Webb D.C. Immunol. Rev., **179**, 173-181, 2001]. Clinically, expression of eotaxin and CCR3 mRNA and protein is observed in the lung tissues of atopic asthmatics and is associated with AHR, reduced FEV₁ and lung eosinophilia [Ying S., Robin D.S., Meng Q., Rottman J., Kennedy R., Ringler D.J., Mackay C.R., Daugherty B.L., Springer M.S., Durham S.R., Williams T.J. and Kay A.B.: Enhanced expression of eotaxin and CCR3 mRNA and protein in atopic asthma. Association with airway hyperresponsiveness and predominant colocalization of eotaxin mRNA to bronchial epithelial and endothelial cells. Eur. J. Immunol., **27**, 3507-3516, 1997; Lamkhieoued Renzi P.M., AbiYounes S., GarciaZepeda E.A., Allakhverdi Z., Ghaffar O., Rothenberg M.D., Luster A.D. and Hamid Q.: Increased expressions of eotaxin in bronchoalveolar lavage and airways of asthmatics contributes to the chemotaxis of eosinophils to the site of inflammation. J.Immunol., **159**: 4593-4601, 1997; Jahnz-Royk K., Plusa T. and Mierzejewska J.: Eotaxin in serum of patients with asthma or

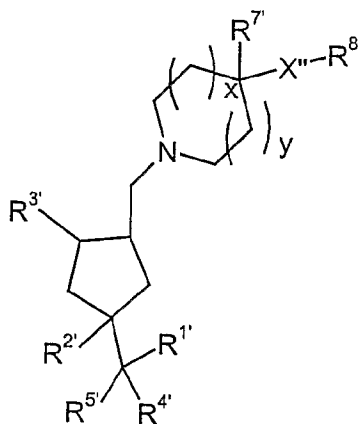
chronic obstructive pulmonary disease: relationship with eosinophil cationic protein and lung function. *Mediators of Inflammation*, 9: 175-179, 2000]. In addition, in allergic rhinitis, CCR3-expressing Th2 lymphocytes co-localize with eosinophils in nasal polyps in close proximity to eotaxin-expressing cells [Gerber B.O., Zanni M.P., Uguccioni M., Loetscher M., Mackay C.R., Pichler W.J., Yawalkar N., Baggiolini M. and Moser B.: Functional expression of the eotaxin receptor CCR3 in T lymphocytes co-localizing with eosinophils. *CURRENT BIOLOGY* 7: 836-843, 1997]. Moreover, viral infections (RSV, influenza virus) which are known risk factors in asthma, result in increased eotaxin expression in lung tissue which is correlated with tissue eosinophilia [Matsukura S., Kokubo F., Kubo H., Tomita T., Tokunaga H., Kadokura M., Yamamoto T., Kuroiwa Y., Ohno T., Suzuki H. and Adachi M.: Expression of RANTES by normal airway epithelial cells after influenza virus A infection. *Am. J. Respir. Cell and Mol. Biol.*, 18: 255-264, 1998; Saito T., Deskin R.W., Casola A., Haeberle H., Olszewska B., Ernest P.B., Alam R., Ogra P.L. and Garofalo R.: Selective regulation of chemokine production in human epithelial cells. *J. Infec. Dis.*, 175: 497-504, 1997].

Thus the binding of CCR3 and related chemokine including eotaxin has been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis, and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis. It is also implicated that binding of CCR3 and related chemokine is an important factor of virus infections including HIV [(Marone G, de Paulis A, Florio G, Petraroli A, Rossi F, Triggiani M.: *Int Arch Allergy Immunol* 2001 Jun;125(2)/89-95), (Li Y et al.: *Blood* 2001 Jun 1; 97(11):3484-90), and (Marone G, Florio G, Petraroli A, Triggiani M, de Paulis A: *Trends Immunol* 2001 May;22 (5):229-32)], lung granuloma (Ruth JH, Lukacs NW, Warmington KS, Polak TJ, Burdick M, Kunkel SL, Strieter RM, Chensue SW: *J Immunol* 1998 Oct 15;161 (8):4276-82), and Alzheimer's diseases (Xia MQ, Qin SX, Wu LJ, Mackay CR, and Hyman BT: *Am J Pathol* 1998 Jul;153 (1):31-37).

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Therefore, CCR3 is an important target and antagonism of CCR3 is likely to be effective in the treatment of such inflammatory and immunoregulatory disorders and diseases.

- 5 WO 00/76514 and WO 00/76513 disclose cyclopentyl modulators of chemokine receptors including CCR3 activity represented by the general formula:



wherein

10

X'' , x , y , $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6 , R^7 , and R^8 , are defined in the application.

Other applications also disclose CCR3 modulators.

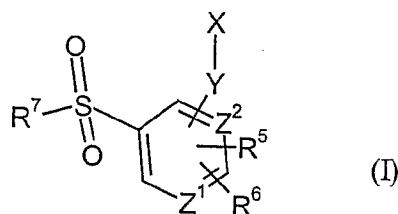
- 15 However, none of the reference and other reference discloses simple sulfonamide derivatives having CCR3 antagonistic activity.

The development of a compound having effective CCR3 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with CCR3
20 activity has been desired.

SUMMARY OF THE INVENTION

As the result of extensive studies on chemical modification of sulfonamide derivatives, the present inventors have found that the compounds of the structure
 5 related to the present invention have unexpectedly excellent CCR3 antagonistic activity. The present invention has been accomplished based on these findings.

This invention is to provide novel sulfonamide derivatives shown by the following
 10 formula (I), its tautomeric and stereoisomeric form, and the salts thereof.



X represents phenyl, which is substituted by 0 to 5 substituents independently
 15 selected from the group consisting of R¹, R², R³, R⁴ and R⁰ or pyridine, which
 is substituted by 0 to 5 substituents independently selected from the group
 consisting of R¹, R², R³ and R⁴

wherein

20 R¹ is hydrogen, halogen, hydroxy, straight- or branched- C₁₋₆ alkyl
 optionally substituted by mono, di or tri halogen, straight- or
 branched- C₁₋₆ alkoxy, straight- or branched- C₁₋₆ alkoxy carbonyl,
 amino, straight- or branched- C₁₋₆ alkylamino, di(straight- or
 25 branched- C₁₋₆ alkyl)amino, straight- or branched- C₁₋₆ alkanoyl, nitro,
 or phenyl,

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R^2 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, or cyano,

5 or

R^1 and R^2 together form benzene ring or C_{5-8} cycloalkyl fused to the adjacent phenyl or pyridine,

10 R^3 is hydrogen, halogen, or straight- or branched- C_{1-6} alkyl,

R^4 is hydrogen, halogen, or straight- or branched- C_{1-6} alkyl,

15 R^0 is hydrogen, halogen, or straight- or branched- C_{1-6} alkyl,

Y represents O, NH, NCH_3 , S, $S(O)$, or SO_2 ;

Z^1 represents CH or N;

20 Z^2 represents CH or N

with the proviso that both Z^1 and Z^2 cannot be N at the same time;

25 R^5 represents hydrogen, halogen, hydroxy, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen or hydroxy, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxy-carbonyl, amino, straight- or branched- C_{1-6} alkanoylamino, phenyl- $(CH_2)_q$ -carbonylamino (wherein q represents an integer selected from 0 to 6), straight- or branched- C_{1-6} alkylbenzoylamino, naphthyl-carbonylamino, thenoylamino, nitro, cyano, carboxy, straight- or

30

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branched- C₁₋₆ alkyl sulfonyl, oxazolidinonyl, or substituents represented by the formula, -SO₂-NR⁵¹R⁵², or -CO-NR⁵¹R⁵²,

wherein

5

R⁵¹ and R⁵² are independently selected from the group consisting of hydrogen, straight- or branched- C₁₋₆ alkyl optionally substituted by cyano or carbamoyl and tetrazolyl optionally substituted by C₁₋₆ alkylnitrile, or

10

R⁵¹ and R⁵² may form, together with the adjacent N, a saturated 5 to 8 membered ring optionally interrupted by NH,

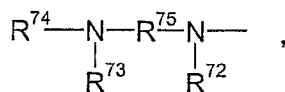
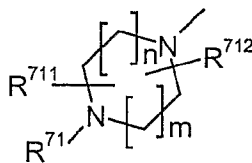
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R⁶ represents hydrogen, halogen, straight or branched C₁₋₆ alkyl optionally substituted by mono di or tri halogen, or straight or branched C₁₋₆ alkoxy, or

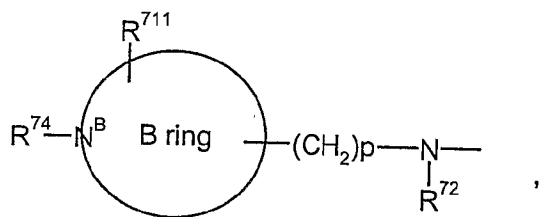
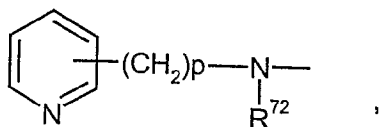
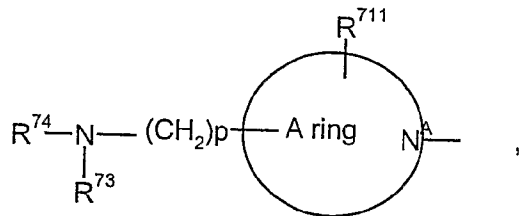
R⁵ and R⁶ may form a pyrrol ring fused to adjacent phenyl, or pyridine; and

R⁷ represents

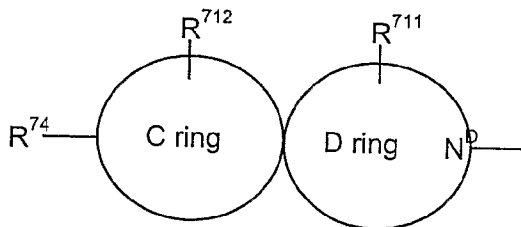
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or



wherein

5 n represents an integer selected from 1 to 3, m represents an integer selected from 0 to 3,

10 R⁷¹ is hydrogen, C₃₋₈ cycloalkyl optionally interrupted by NH, N-CH₃ or O, straight- or branched C₁₋₆ alkoxy carbonyl, phenyl optionally substituted by straight- or branched C₁₋₆ alkyl, benzyl, formyl, or

straight- or branched C₁₋₆ alkyl

5 wherein the alkyl is optionally substituted by hydroxy, straight- or branched- C₁₋₆ alkoxy, hydroxy straight- or branched- C₁₋₆ alkoxy, carboxy, straight- or branched- C₁₋₆ alkoxycarbonyl, straight- or branched- C₁₋₆ alkylthio, di(straight- or branched- C₁₋₆ alkyl)amino, mono, di or tri halogen, or C₃₋₈ cycloalkyl optionally interrupted by NH or O,

10 R⁷¹¹ and R⁷¹² are independently selected from the group consisting of hydrogen, halogen, hydroxy, carboxy, cyano, straight- or branched C₁₋₆ alkyl optionally substituted by hydroxy, carboxy, or mono, di or tri halogen, carbamoyl, di (straight- or branched C₁₋₆ alkyl)amino carbonyl, and -NR^{711a}R^{711b}

15 wherein

R^{711a} and R^{711b} are independently selected from the group consisting of hydrogen, straight- or branched- C₁₋₆ alkyl, straight- or branched- C₁₋₆ alkanoyl, and straight- or branched- C₁₋₆ alkyl-sulfonyl, or

20 R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

25 R⁷² is hydrogen, or straight- or branched- C₁₋₆ alkyl;

R⁷³ is hydrogen, or straight- or branched- C₁₋₆ alkyl,

R⁷⁴ is hydrogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by phenyl, or

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R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally substituted by C_{1-6} alkyl and optionally interrupted by NH or O;

5 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

10 A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

15 C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

20 A 7 to 12 membered diazabicyclic ring stands for a saturated bicyclic ring system consisting of 5 to 10 carbon atoms and 1 to 2 nitrogen atoms, wherein said bicyclic ring system does not exhibit a spiro ring connection. Preferred are 8 to 10 membered ring systems.

25 This invention is also to provide a method for treating or preventing a CCR3 related disorder or disease in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the sulfonamide derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

30 Further this invention is to provide a use of the sulfonamide derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt

thereof in the preparation of a medicament for treating or preventing a CCR3 related disorder or disease.

5 The compounds of the present invention surprisingly show excellent CCR3 antagonistic activity. They are, therefore suitable for the production of medicament or medical composition, which may be useful to treat CCR3 related diseases.

10 More specifically, since the compounds of the present invention antagonise CCR3, they are useful for treatment and prophylaxis of diseases as follows:

asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

15 Therefore, CCR3 is an important target and antagonism of CCR3 is likely to be effective in the treatment and prophylaxis of such inflammatory and immunoregulatory disorders and diseases.

20 The compounds of the present invention are also useful for treatment and prophylaxis of diseases like virus infections including HIV, lung granuloma, and Alzheimer's diseases, since the diseases also relate to CCR3.

In another embodiment, the compounds of formula (I) are those wherein:

25 X, Y, Z¹, Z², R¹, R², R³, R⁴, R⁰ and R⁷ are as defined above,

R⁵ is chloro, iodo, nitro, or cyano, and

R⁶ is hydrogen.

30 In another embodiment, the compounds of formula (I) are those wherein:

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X, Y, Z¹ and Z² are as defined above,

R¹ is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono,
di or tri halogen;

5

R² is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono,
di or tri halogen;

R³ is hydrogen;

10

R⁴ is hydrogen;

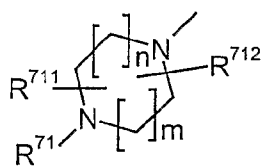
R⁰ is hydrogen;

15 R⁵ is halogen, nitro, or cyano;

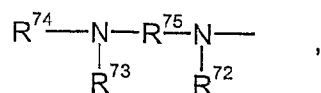
R⁶ is hydrogen; and

R⁷ represents

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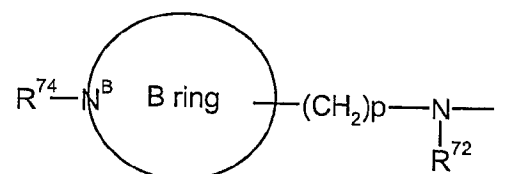
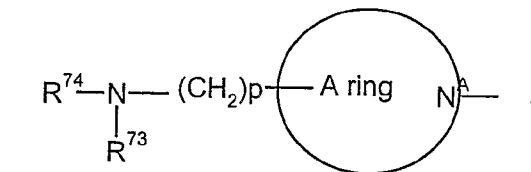


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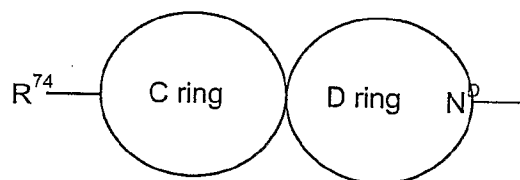


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or



wherein

5 n represents an integer selected from 1 to 3, m represents an integer selected from 0 to 3,

10 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxy carbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

15 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, carboxy, or straight- or branched C_{1-6} alkyl, or

R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl,

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R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,

R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or

5

R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

10

p represents an integer selected from 0 to 4;

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

15

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

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In another embodiment, the compounds of formula (I) are those wherein:

X, Y, Z^1 and Z^2 are as defined above,

25

R^1 and R^2 are identical or different and represent chloro, or methyl;

R^3 is hydrogen or fluoro;

R^4 is hydrogen;

30

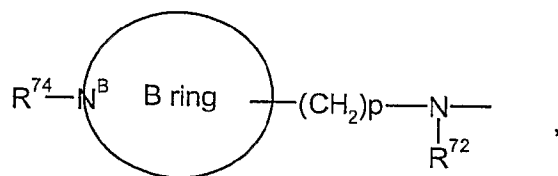
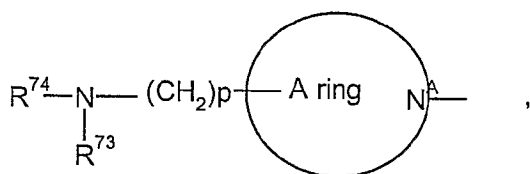
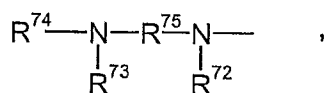
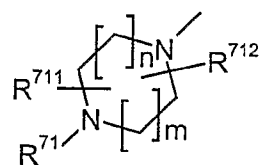
- 15 -

R^0 is hydrogen;

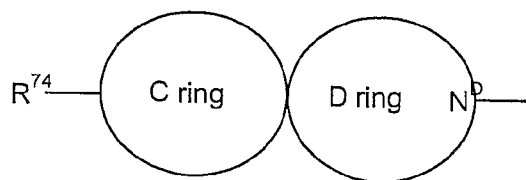
R^5 is chloro, iodo, nitro, or cyano;

5 R^6 is hydrogen; and

R^7 represents



or



wherein

- 16 -

- n represents an integer selected from 1 to 3, m represents an integer selected from 0 to 3,
- 5 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,
- 10 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, carboxy, or straight-or branched C_{1-6} alkyl, or
- R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;
- 15 R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;
- R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,
- 20 R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or
- R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;
- 25 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;
- p represents an integer selected from 0 to 4;
- 30 A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

- 17 -

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

5 C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

In another embodiment, the compounds of formula (I) are those wherein:

X, Y, Z¹ and Z² are as defined above,

10

R¹ is hydrogen, fluoro, chloro, bromo, methyl, isopropyl, butyl, tert-butyl, trifluoromethyl, methoxy, amino, dimethylamino, acetyl, or nitro;

15

R² is hydrogen, fluoro, chloro, methyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, or cyano;

R³ is hydrogen or fluoro;

R⁴ is hydrogen;

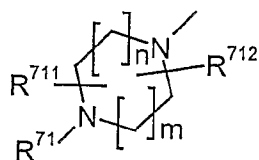
20

R⁰ is hydrogen;

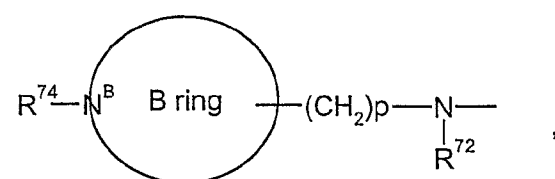
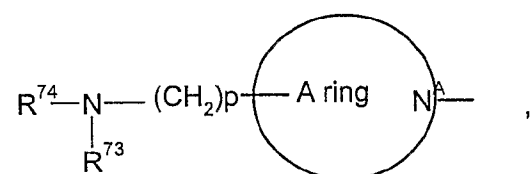
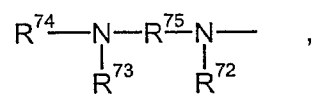
R⁵ is chloro, iodo, nitro, or cyano;

25 R⁶ is hydrogen; and

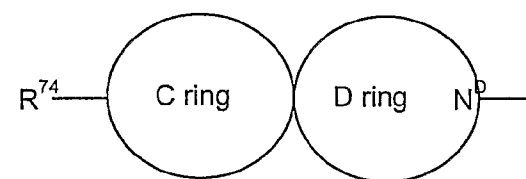
R⁷ represents



- 18 -



or



wherein

n represents an integer 1,

5 m represents an integer selected from 1 or 2,

 R^{71} represents hydrogen, methyl, ethyl or isopropyl; R^{711} represents hydrogen, methyl, or carboxy

10

 R^{712} represents hydrogen or methyl, or

- 19 -

R^{71} and R^{711} may form, together with the adjacent N atom, a 5 membered saturated ring;

5 R^{72} is hydrogen, methyl, or ethyl;

R^{73} is hydrogen, or methyl,

R^{74} is hydrogen, methyl, or ethyl, or

10 R^{73} and R^{74} may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

R^{75} is phenyl;

15 p represents an integer selected from 0 to 4;

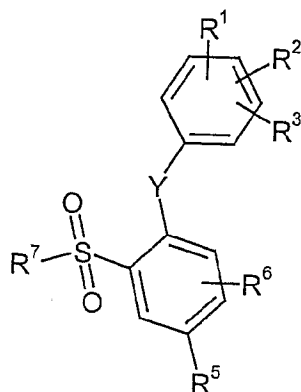
A ring represents piperidino, or pyrrolidino;

B ring represents pyrrolidino; and

20

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

Yet other preferred compounds of formula (I) represent formula (I-2) and are those



(I-2)

wherein

5 R^1 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxy carbonyl, amino, straight- or branched- C_{1-6} alkylamino, di(straight- or branched- C_{1-6} alkyl)amino, straight- or branched- C_{1-6} alkanoyl, or nitro,

10 R^2 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, or cyano, or

R^1 and R^2 may form benzene ring or C_{5-8} cycloalkyl fused to the adjacent phenyl;

15 R^3 is hydrogen or halogen,

Y represents O, NH, NCH_3 , S, $S(O)$, or SO_2 ;

20 R^5 is hydrogen, halogen, hydroxy, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di, or tri halogen or hydroxy, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxycarbonyl, amino, straight- or branched- C_{1-6} alkanoylamino, phenyl- $(CH_2)_q$ -carbonylamino (wherein q represents an integer selected from 0 to 6), straight- or branched- C_{1-6} alkyl-benzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, carboxy, straight- or branched- C_{1-6} alkyl sulfonyl, oxazolidinonyl, or substituents
25 represented by the formula, $-SO_2-NR^{51}R^{52}$, or $-CO-NR^{51}R^{52}$,

wherein

30 R^{51} and R^{52} are identical or different and represent hydrogen, straight- or branched- C_{1-6} alkyl optionally substituted by cyano or carbamoyl, tetrazolyl optionally substituted by C_{1-6} alkyl nitrile, or R^{51} and R^{52}

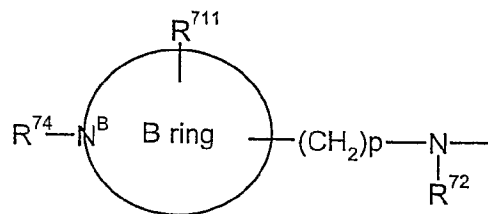
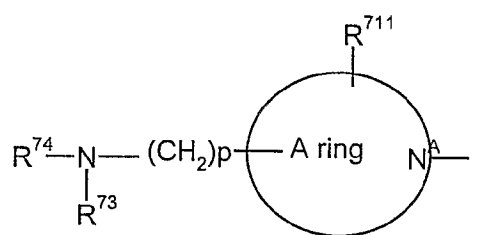
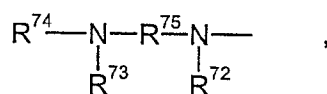
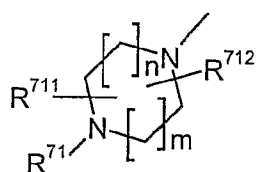
- 21 -

may form, together with the adjacent N, a saturated 5 to 8 membered ring optionally interrupted by NH,

5 R^6 is hydrogen, halogen, straight or branched C_{1-6} alkyl optionally substituted by mono, di or tri halogen, or straight or branched C_{1-6} alkoxy, or

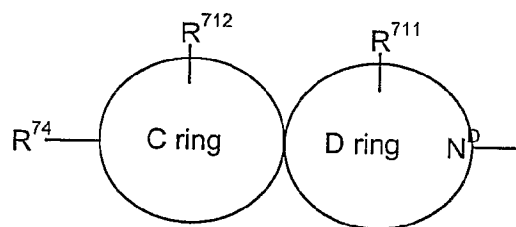
R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl; and

10 R^7 represents



- 22 -

or



wherein

n represents an integer selected from 1 to 3, m represents an integer selected from 0 to 3,

5

R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

10

R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carboxy, cyano, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono, di or tri halogen, carbamoyl, di (straight- or branched C_{1-6} alkyl)amino carbonyl, or $-NR^{711a}R^{711b}$

15

wherein

20

R^{711a} and R^{711b} are independently selected from the group consisting of hydrogen, straight- or branched- C_{1-6} alkyl, straight- or branched- C_{1-6} alkanoyl, or straight- or branched- C_{1-6} alkylsulfonyl, or

- 23 -

R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R⁷² is hydrogen, or straight- or branched- C₁₋₆ alkyl;

R⁷³ is hydrogen, or straight- or branched- C₁₋₆ alkyl,

R⁷⁴ is hydrogen, or straight- or branched- C₁₋₆ alkyl, or

R⁷³ and R⁷⁴ may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

R⁷⁵ is straight- or branched- C₁₋₆ alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

Yet other preferred compounds of formula (I-2) are those wherein:

R¹ is hydrogen, halogen, straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C₁₋₆ alkoxy, straight- or

- 24 -

branched- C₁₋₆ alkoxy carbonyl, amino, straight- or branched- C₁₋₆ alkyl-amino, di(straight- or branched- C₁₋₆ alkyl)amino, straight- or branched- C₁₋₆ alkanoyl, or nitro,

- 5 R² is hydrogen, halogen, straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen, straight- or branched-C₁₋₆ alkoxy, or cyano, or

R¹ and R² may form benzene ring or C₅₋₈ cycloalkyl fused to the adjacent phenyl;

- 10 R³ is hydrogen or halogen,

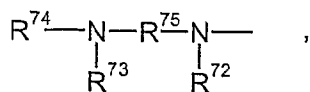
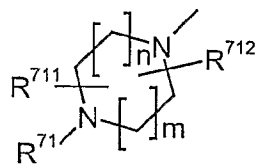
Y represents O, NH, NCH₃, S, S(O), or SO₂;

R⁵ is chloro, iodo, nitro, or cyano;

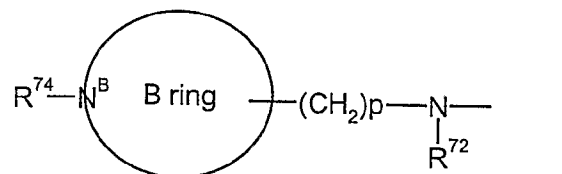
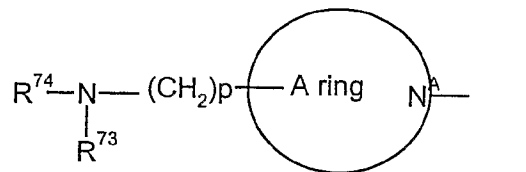
15

R⁶ is hydrogen; and

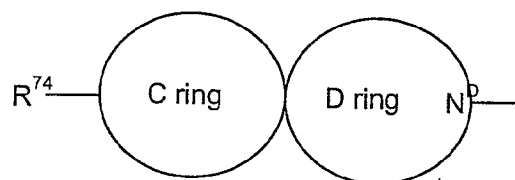
R⁷ represents



- 25 -



or



wherein

5

n represents an integer selected from 1 to 3, m represents an integer selected from 0 to 3,

10 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

15 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, carboxy, or straight-or branched C_{1-6} alkyl, or

R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

- 26 -

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;

R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,

5 R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or

R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

10 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

15 A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

20

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

In another embodiment, the compounds of formula (I-2) are those wherein :

25 R^1 is hydrogen, halogen, or straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen;

R^2 is hydrogen, halogen, or straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen;

30

R^3 is hydrogen or halogen,

- 27 -

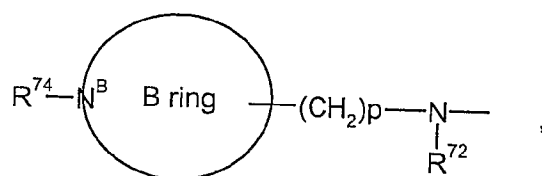
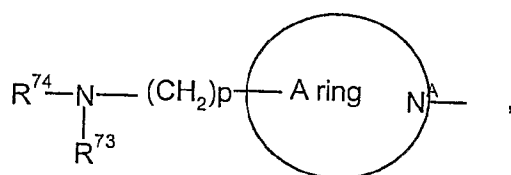
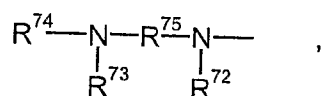
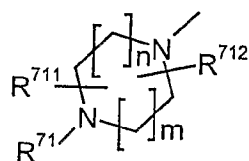
Y is O, NH, NCH₃, S, S(O), or SO₂;

R⁵ is halogen, nitro, or cyano;

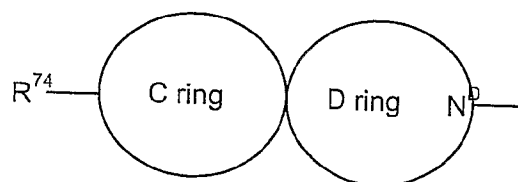
5

R⁶ is hydrogen; and

R⁷ represents



or



wherein

- n represents an integer selected from 1 to 3,
- m represents an integer selected from 0 to 3,
- 5 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,
- 10 R^{711} represents hydrogen, methyl, or carboxy,
- R^{712} represents hydrogen or methyl, or
- 15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;
- R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;
- 20 R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,
- R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or
- 25 R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;
- R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;
- 30 p represents an integer selected from 0 to 4;

- 29 -

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

5 B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

10 In another embodiment, the compounds of formula(I-2) are those wherein:

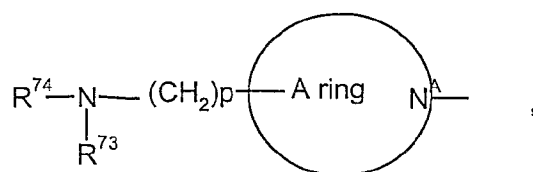
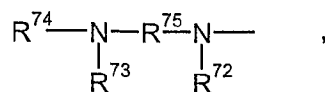
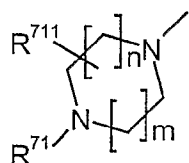
R^1 , R^2 and R^3 are identical or different and represent hydrogen, chloro, or methyl;

Y is O, NH, NCH_3 , S, $S(O)$, or SO_2 ;

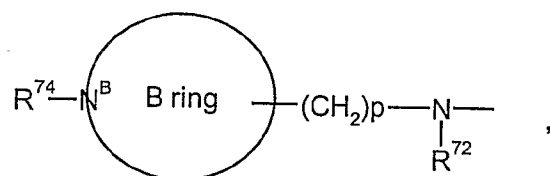
15 R^5 is chloro, iodo, nitro, or cyano;

R^6 is hydrogen; and

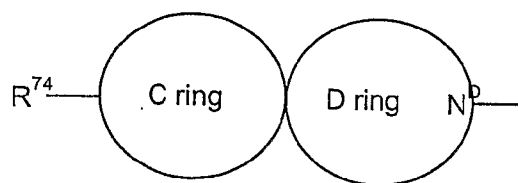
R^7 represents



- 30 -



or



wherein

n represents an integer selected from 1 to 3,

5 m represents an integer selected from 1 to 3,

10 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxy carbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

R^{711} represents hydrogen, methyl, or carboxy or

15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;

20 R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl;

- 31 -

R⁷⁴ is hydrogen, or straight- or branched- C₁₋₆ alkyl; or

R⁷³ and R⁷⁴ may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

5

R⁷⁵ is straight- or branched- C₁₋₆ alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

10

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

15

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

In another embodiment, the compounds of formula (I-2) are those wherein

20

R¹ is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

R² is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

25

R³ is hydrogen or fluoro;

Y is O, NH, NCH₃, S, S(O), or SO₂;

30

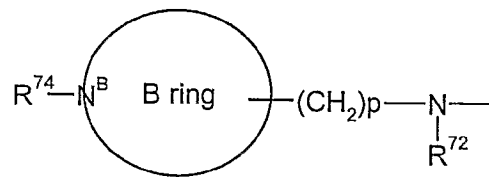
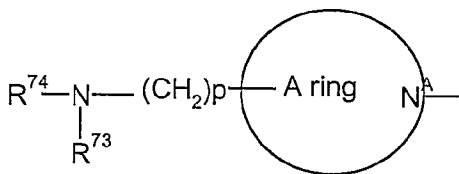
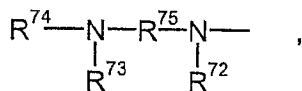
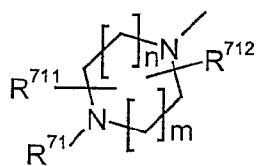
- 32 -

R^5 is hydrogen, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, methoxy, amino, acetylamino, isobutylcarbonylamino, tert-butylcarbonylamino, benzoylamino, benzylcarbonylamino, phenethylcarbonylamino, methylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, methylsulfonyl, dimethylaminosulfonyl, piperazinosulfonyl, dimethylaminocarbonyl, or piperazinocarbonyl;

R^6 is hydrogen, methyl, or methoxy; or

R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl; and

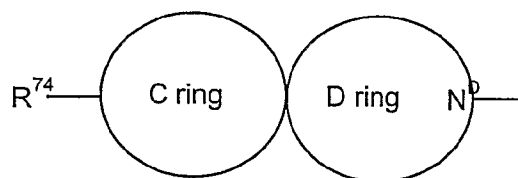
R^7 represents



15

- 33 -

or



wherein

n represents an integer 1,

5

m represents an integer 1 or 2,

R⁷¹ is hydrogen, methyl, ethyl, isopropyl, sec-butyl, branched pentyl, hydroxyethyl, hydroxyethoxyethyl, cyclopentyl, cyclohexyl, tert-butoxycarbonyl, phenyl, tolyl, benzyl, or formyl,

10

R⁷¹¹ represents hydrogen, methyl, or carboxy,

R⁷¹² represents hydrogen or methyl, or

15

R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 membered saturated ring;

R⁷² is hydrogen, methyl, or ethyl;

20

R⁷³ is hydrogen, or methyl,

R⁷⁴ is hydrogen, methyl, or ethyl, or

25

R⁷³ and R⁷⁴ may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

- 34 -

R⁷⁵ is phenyl;

p represents an integer selected from 0 to 4;

5 A ring represents piperidino, or pyrrolidino;

B ring represents pyrrolidino; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

10

In another embodiment, the compounds of formula (I-2) are those wherein;

R¹ is hydrogen, fluoro, chloro, bromo, methyl, isopropyl, butyl, tert-butyl, tri-fluoromethyl, methoxy, amino, dimethylamino, acetyl, or nitro;

15

R² is hydrogen, fluoro, chloro, methyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, or cyano;

R³ is hydrogen or fluoro;

20

Y is O, NH, NCH₃, S, S(O), or SO₂;

R⁵ is hydrogen, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, methoxy, amino, acetilamino, isobutylcarbonylamino, tert-butylcarbonylamino, benzoyl-amino, benzylcarbonylamino, phenethylcarbonylamino, methylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, methylsulfonyl, dimethyl-aminosulfonyl, piperazinosulfonyl, dimethylaminocarbonyl, or piperazino-carbonyl;

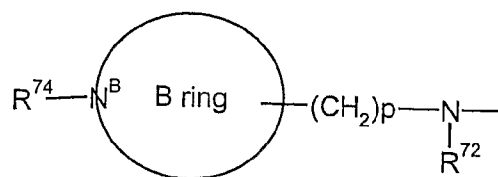
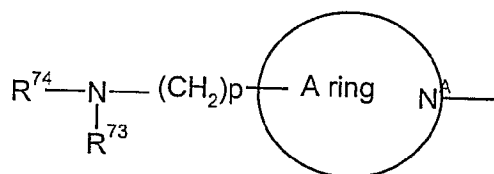
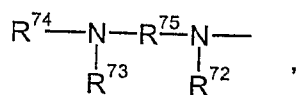
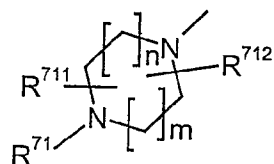
25

30 R⁶ is hydrogen, methyl, or methoxy; or

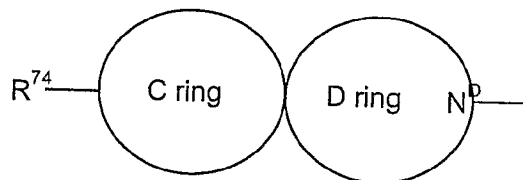
- 35 -

R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl, and

R^7 represents



or



wherein

5

n represents an integer 1,

m represents an integer 1 or 2,

- 36 -

R^{71} represents hydrogen, methyl, ethyl, isopropyl, sec-butyl, branched pentyl, hydroxyethyl, hydroxyethoxyethyl, cyclopentyl, cyclohexyl, tert-butoxycarbonyl, phenyl, tolyl, benzyl, or formyl,

5 R^{711} represents hydrogen, methyl, or carboxy

R^{712} represents hydrogen or methyl, or

10 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 membered saturated ring;

R^{72} is hydrogen, methyl, or ethyl,

15 R^{73} is hydrogen, or methyl,

R^{74} is hydrogen, methyl, or ethyl, or

20 R^{73} and R^{74} may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

R^{75} is phenyl;

p represents an integer selected from 0 to 4;

25 A ring represents piperidino, or pyrrolidino;

B ring represents pyrrolidino; and

30 C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

In another embodiment, the compounds of formula (I-2) are those wherein;

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R^1 is chloro, bromo, or methyl;

R^2 is hydrogen, chloro, bromo, or methyl;

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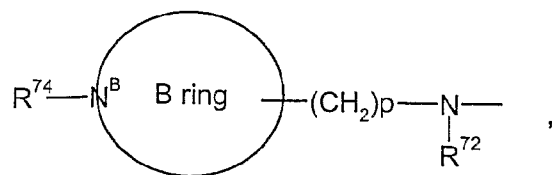
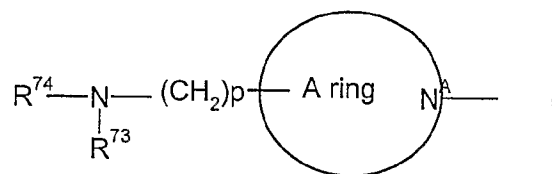
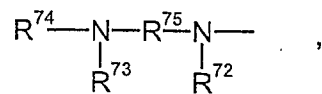
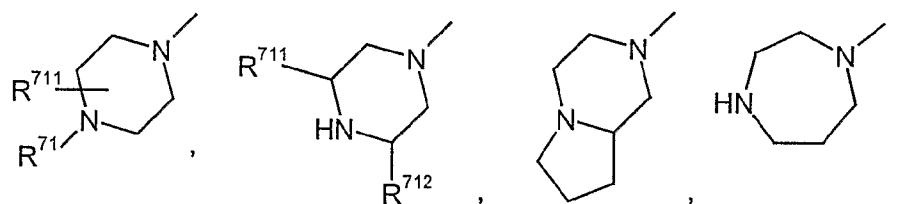
R^3 is hydrogen or fluoro;

Y represents O, S, or S(O);

10 R^5 represents hydrogen, chloro, nitro, or cyano;

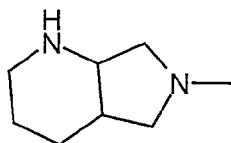
R^6 represents hydrogen;

R^7 represents



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or



wherein

R^{71} represents hydrogen, methyl, ethyl or isopropyl;

5 R^{711} represents hydrogen, methyl, or carboxy;

R^{712} represents hydrogen or methyl;

10 R^{72} is hydrogen, methyl, or ethyl;

R^{73} is hydrogen, methyl, or ethyl;

R^{74} is hydrogen, methyl, or ethyl; or

15 R^{73} and R^{74} may form, together with adjacent N atom, piperidino, or pyrrolidino,

R^{75} is phenyl;

20 p represents integer 0 or 1;

A ring represents piperidino, or pyrrolidino; and

B ring represents pyrrolidino.

25

The preferable compounds of the present invention are as follows:

- 1- {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-4-ethylpiperazine,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
- 5 1- {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-4-isopropylpiperazine,
- 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
- 1- {[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-4-ethylpiperazine,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-4-(1-pyrrolidinyl)piperidine,
- 4-(3,5-dichlorophenoxy)-3- {[4-(1-pyrrolidinyl)-1-piperidinyl]sulfonyl} benzonitrile,
- 10 4-(3,5-dichlorophenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-N,N-diethyl-3-pyrrolidinamine,
- (2S)-1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-2-(1-pyrrolidinylmethyl)-pyrrolidine,
- 3-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylsulfonyl]-4-(3,5-dichloro-
- 15 phenoxy)benzonitrile,
- 4-[(3,5-dichlorophenyl)sulfanyl]-3-(1-piperazinylsulfonyl) benzonitrile,
- 4-[(3,5-dichlorophenyl)sulfinyl]-3-(1-piperazinylsulfonyl) benzonitrile,
- 1- {[2-(3,5-dibromophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
- 1- {[2-(3,5-dichloro-2-fluorophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
- 20 1- {[5-cyano-2-(3,5-dichlorophenoxy)phenyl]sulfonyl}-2-piperazinecarboxylic acid,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-2-piperazinecarboxylic acid,
- 1- {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-1,4-diazepane,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-1,4-diazepane,
- 1- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-3,5-dimethylpiperazine,
- 25 3-(1,4-diazepan-1-ylsulfonyl)-4-(3,5-dichlorophenoxy) benzonitrile,
- 1'- {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-1,3'-bipyrrolidine,
- 3-(1,3'-bipyrrolidin-1'-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile,
- 1- {[2-[(3,5-dichlorophenyl)sulfanyl]-5-nitrophenyl]sulfonyl}-4-(1-pyrrolidinyl)piperidine,
- 4-(3,5-dichlorophenoxy)-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylsulfonyl)benzo-
- 30 nitrile, and
- 3-(1,4-diazepan-1-ylsulfonyl)-4-[(3,5-dichlorophenyl)sulfanyl]benzonitrile,

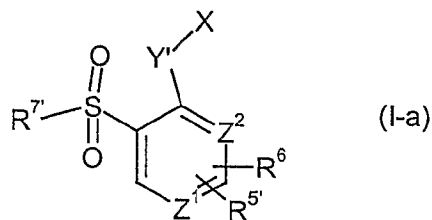
- 40 -

and their tautomeric and stereoisomeric form, and physiologically acceptable salts thereof.

5 The compound of the formula (I) of the present invention can be prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups
 10 are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

The compound represented by the general formula (I-a) can be prepared by the Reaction A or A' below.

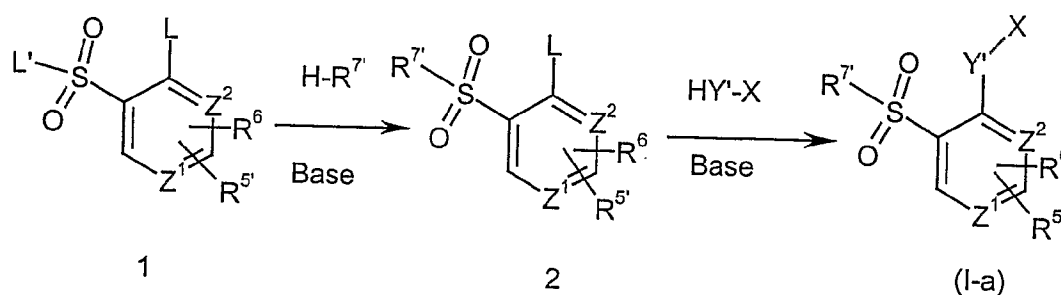
15



wherein

20 X, Z¹, Z² and R⁶ are as defined above, Y' is O, NH, or S, R^{5'} is nitro, C₁₋₆ alkyl, C₁₋₆ alkylsulfonyl, carboxy and R^{7'} is the same as R⁷ as defined above or protected R⁷.

Reaction A



Compound 1 (wherein L and L' are identical or different and represent leaving group, such as halogen atom e.g., fluorine, chlorine, bromine, or iodine atom; C₆₋₁₀ aryl-sulfonyloxy group e.g., benzenesulfonyloxy, or p-toluenesulfonyloxy; and C₁₋₄ alkyl-sulfonyloxy group, e.g., trifluoromethanesulfonyloxy, methanesulfonyloxy and the like) and H-R^{7'} can be reacted to obtain compound 2 in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethyl sulfoxide, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

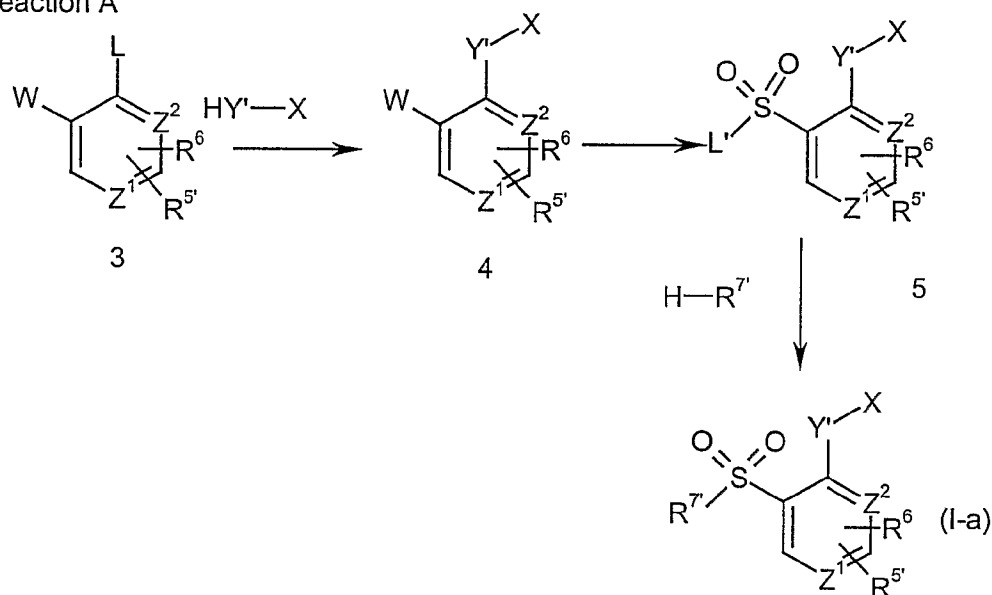
The reaction temperature is usually, but not limited to, about -10°C to 200°C, and preferably about 10°C to 80°C. The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 hr to 24 hrs.

The reaction can be advantageously conducted in the presence of a base. The examples of the base include an alkali metal hydride such as sodium hydride or potassium hydride; alkali metal alkoxide such as sodium methoxide, sodium ethoxide and potassium tert-butoxide; alkali metal hydroxide such as sodium hydroxide and potassium hydroxide; carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium

hydrogen carbonate; organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

Then compound 2 and $\text{HY}'\text{-X}$ (wherein X and Y' are the same as defined above) can be reacted in a similar manner as that of the reaction of A-1 and $\text{H-R}^{7'}$ to obtain the compound (I-a).

Reaction A'



Compound 3 (wherein L is identical or different and represent leaving group, such as halogen atom e.g., fluorine, chlorine, bromine, or iodine atom; C₆₋₁₀ arylsulfonyloxy group e.g., benzenesulfonyloxy, or p-toluenesulfonyloxy; and C₁₋₄ alkylsulfonyloxy group, e.g., trifluoromethanesulfonyloxy, methanesulfonyloxy and the like, W represents nitro, halogen, thiol, C₁₋₆ alkyl sulfinyl, sulfinic acid, sulfonic acid, sulfonamide and the like) and $\text{HY}'\text{-X}$ can be reacted to obtain compound 4 in a similar manner as that for the preparation of I-a from compound 2 and $\text{HY}'\text{-X}$.

Compound 4 can be converted to compound 5 (wherein L' is as defined above) by known method in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether,

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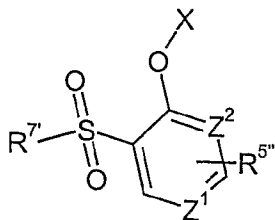
isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); organic acid such as acetic acid; inorganic acid such as HCl and H₂SO₄;
 5 water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to about -10°C to 200°C, and preferably about 10°C to 80°C. The reaction may be carried out for, usually, 30
 10 minutes to 48 hrs and preferably 1 to 24 hrs.

Then compound 5 and H-R^{7'} can be reacted to obtain (I-a) in a similar manner as that for the preparation of compound 2 from compound 1 and H-R^{7'}.

15 The compound (I-a) can be further reacted to modify R^{7'}, e.g. to deprotect, or to modify R^{5'} to obtain the compound having amino, halogen, hydroxy, cyano, C₁₋₆ alkoxy or amide group.

Alternatively, the compound represented by the general formula (I-b) can be prepared
 20 by the Reaction B below.

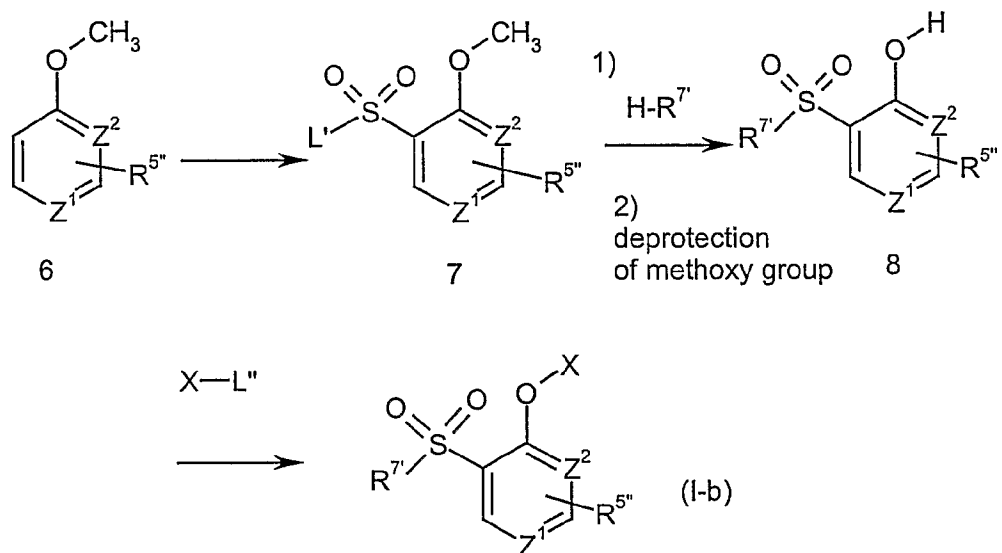


(I-b)

wherein

25 X, Z¹ and Z² are as defined above, R^{5''} is halogen, carboxy or nitro and R^{7'} is the same as R⁷ as defined above or protected R⁷.

Reaction B



Reaction B is especially advantageous when $R^{5''}$ is Br.

- 5 First, compound 6 and sulfonic acid halide (e.g., chlorosulfonic acid) or equivalent thereof can be reacted to obtain compound 7 (wherein L' is as defined above) in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; nitriles such as aceto-
- 10 nitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.
- 15 The reaction temperature is usually, but not limited to, about -10°C to 200°C , and preferably about 10°C to 80°C . The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs.

20 Compound 8 can be prepared from compound 7 in two steps; (step 1) the reaction with $\text{H-R}^{7'}$ and (step 2) deprotection of methoxy group. (step 1) The reaction of

compound 7 and H-R^{7'} can be performed in a similar manner as that for the preparation of compound 2 from compound 1 and H-R^{7'}.

5 (Step 2) The successive deprotection of methoxy group to obtain B-3 can be done by the reaction with Lewis acid such as, for example, BBr₃, in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

10

The reaction temperature is usually, but not limited to about -10°C to 200°C, and preferably about 10°C to 80°C. The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs.

15 Then compound 8 can be reacted with X-L^{8'} (wherein X is defined as above, L^{8'} represents leaving group, such as boronic acid, halogen atom e.g., fluorine, chlorine, bromine, or iodine atom) to obtain the compound (I-b). The reaction can be performed in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethyl sulfoxide, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

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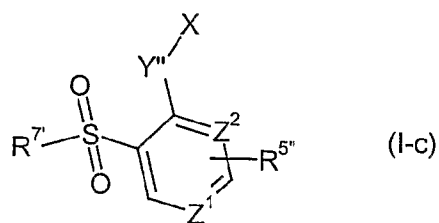
The reaction temperature is usually, but not limited to about -10°C to 200°C, and preferably about 10°C to 100°C. The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs. The reaction can be carried out in the presence of a catalyst, including for instance, copper salts such as copper(II) acetate, palladium salts such as palladium (II) acetate, and others. The reaction can be

30

advantageously conducted in the presence of a base. The examples of the base include an alkali metal alkoxide such as sodium methoxide, sodium ethoxide and potassium tert-butoxide; alkali metal hydroxide such as sodium hydroxide and potassium hydroxide; carbonates such as cesium carbonate, sodium carbonate and potassium carbonate; alkali metal hydrogen carbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

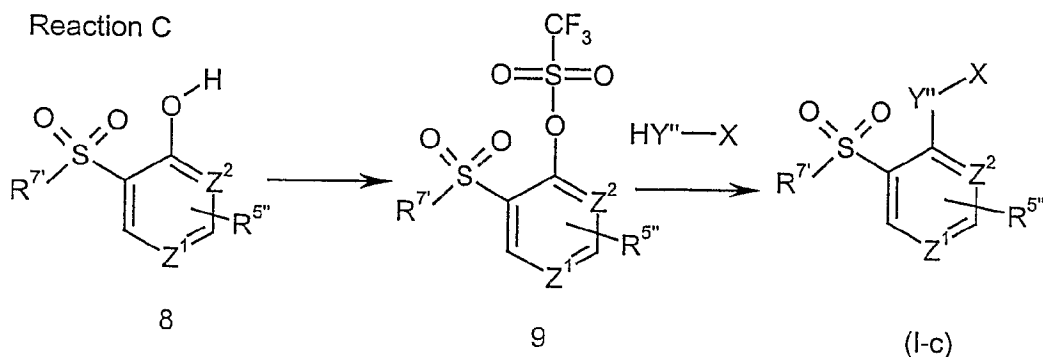
The compound (I-b) can be further reacted to modify $R^{7'}$, e.g. to deprotect, or to modify $R^{5''}$ to obtain the compound having amino, halogen, hydroxy, cyano, C_{1-6} alkoxy or amide group.

The compound (I-c) below can be advantageously prepared by the Reaction C below.



wherein

X , Z^1 , Z^2 and $R^{5''}$ are as defined above, Y'' is NH or S, and $R^{7'}$ is the same as R^7 as defined above or protected R^7 .



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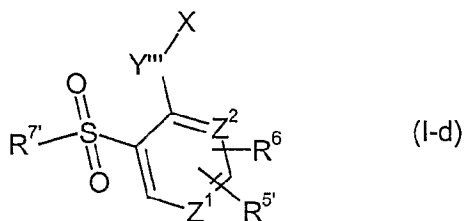
First, compound 8, which can be prepared as described in the Reaction B can be reacted with either trifluoromethanesulfonic anhydride or trifluoromethanesulfonic chloride to obtain compound 9. The reaction can be performed in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; sulfoxides such as dimethyl sulfoxide, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to about -10°C to 200°C , and preferably about 0°C to 100°C . The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs. The reaction can be advantageously conducted in the presence of a base. The examples of the base include organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, and others.

Then compound 9 and $\text{HY}''\text{-X}$ can be reacted to obtain compound (I-c) in a similar manner as that for I-a from compound 2 and $\text{HY}'\text{-X}$.

The compound (I-c) can be further reacted to modify $\text{R}^{7'}$, e.g. to deprotect, or to modify $\text{R}^{5''}$ to obtain the compound having amino, halogen, hydroxy, cyano, C_{1-6} alkoxy or amide group.

The compound (I-d) below can be prepared by the Reaction D below.

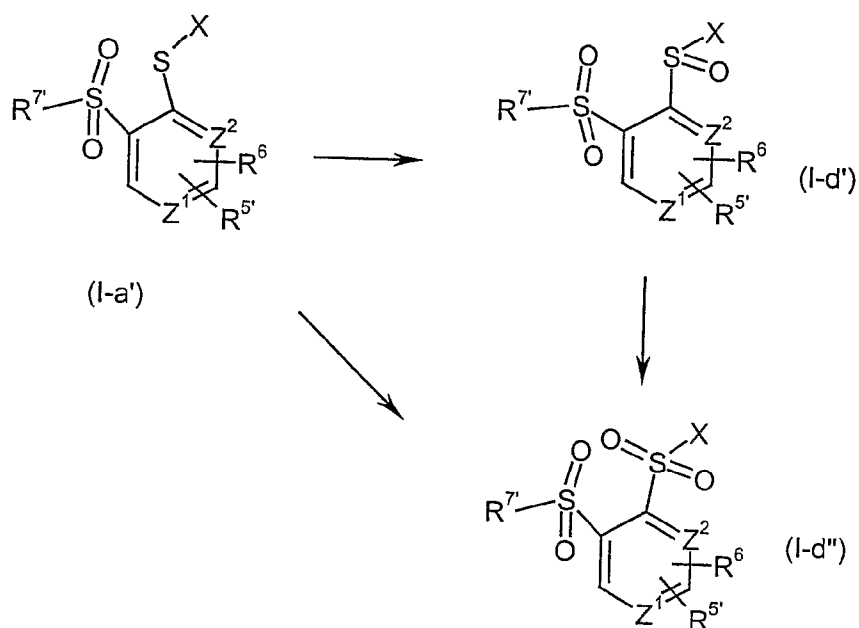


wherein

X, Z¹, Z², R^{5'} and R⁶ are as defined above, Y''' is SO or SO₂ and R^{7'} is the same as R⁷ as defined above or protected R⁷.

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Reaction D



The sulfoxide compounds of the formula (I-d') can be prepared by oxidation of compound (I-a') using appropriate oxidant including but not limited to, peroxide, such as hydrogen peroxide, t-butyl peroxide; peracids such as meta-chloroperbenzoic acid and the like. The reaction can be performed in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

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The reaction temperature is usually, but not limited to about -10°C to 200°C , and preferably about 0°C to 100°C . The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs.

- 5 The sulfone compounds of the formula (I-d'') can be prepared by oxidation of compound (I-a') with an oxidant such as, for example, sodium periodate (NaIO_4) or sodium hypochlorite (NaOCl) in the presence of catalyst such as, for instance, ruthenium (III) chloride.
- 10 The reaction can be performed in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; water and others. Optionally, two or
- 15 more of the solvents selected from the listed above can be mixed and used. The reaction temperature is usually, but not limited to about -10°C to 200°C , and preferably about 0°C to 100°C . The reaction may be carried out for, usually, 30 minutes to 48 hrs and preferably 1 to 24 hrs.
- 20 The sulfone compounds of the formula (I-d'') can also be prepared by oxidation of compound (I-d') in a similar manner as that for the oxidation of compound (I-a').

The compound (I-d') and (I-d'') can be further reacted to modify $\text{R}^{7'}$, e.g., to deprotect, or to modify $\text{R}^{5'}$ to obtain the compound having amino, halogen, hydroxy, cyano, C_{1-6} alkoxy or amide group.

25

When the compound shown by the formula (I) or a salt thereof has tautomeric isomers and/or stereoisomers (e.g., geometrical isomers and conformational isomers), each of their separated isomer and mixtures are also included in the scope of the

30 present invention.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

- 5 Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.
- 10 Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.
- 15 Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane,
- 20 and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.
- 25 The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.
- 30 The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols

and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via
5 topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including,
10 without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

15 The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

20 Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations
25 of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a
30 diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions,

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solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

5 For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose,
10 agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium
15 stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a
20 carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

25 Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

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The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in suitable oil.

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The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A “unit dose” is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

10

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

20

EXAMPLES

5 The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

10 ¹H NMR spectra were recorded using either Bruker DRX-300 (300MHz for ¹H) spectrometer in CDCl₃. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectroscopy data were
15 recorded on a FINNIGAN MAT 95. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150μm)) was used for all column chromatography separations.

20 All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Kanto Chemical Co., Ltd.

25 The effects of the present compounds were examined by the following assays and pharmacological tests.

[Determination of IC₅₀ values of compounds in receptor binding assay]

(1) cell

5 Human CCR3-transformed K562 cells were used. The cloned CCR3 cDNA was constructed with pcDNA3 vector and transfected into a K562 cell line. The human CCR3-transformed K562 cells were maintained in RPMI-1640 (Cat.#22400-089, Life Technologies) supplemented with 10% FCS (Cat.#A-1115-L, Hyclone), 55 μ M 2-mercaptoethanol (Cat.#21985-023, Life Technologies), 1 mM sodium pyruvate (Cat.#11360-070, Life Technologies), 100 units/ml of penicillin G and 100 μ g/ml of streptomycin (Cat.#15140-122, Life Technologies), and 0.4 mg/ml of Geneticin (Cat.#10131-035, Life Technologies)(hereinafter called "culture medium"). Before the receptor binding assay, cells were pretreated with 5 mM sodium butyrate (Cat.#193-01522, Wako)-containing the culture medium (2×10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Receptor binding assay (RBA)

20 Butyrate-pretreated cells, suspended in binding buffer (25 mM HEPES pH 7.6, 1 mM CaCl₂, 5 mM MgCl₂, 0.5% BSA, 0.1% NaN₃) at a cell density of 2×10^6 cells/ml, were added into 60 μ l/well in the 96-well round bottom polypropylene plate (Cat.#3365, Costar). Compounds, diluted with the binding buffer (4-times higher concentration of the final concentration), were added into 30 μ l/well in the polypropylene plate. [¹²⁵I]-labeled human eotaxin (Cat.#IM290, Amersham Pharmacia Biotech), diluted with the binding buffer at the concentration of 0.4 nM (final concentration; 0.1 nM), was added into 30 μ l/well in the polypropylene plate. Total 120 μ l/well of binding reaction mixture (60 μ l/well of cell suspension, 30 μ l/well of compound solution, and 30 μ l/well of [¹²⁵I]-labeled eotaxin) were incubated in the polypropylene plate for 1 hour at room temperature after the incubation,

- 100 μ l/well of the reaction mixture was transferred to a filtration plate (Cat.#MAFB-N0B, Millipore), and washed with the washing buffer (25 mM HEPES pH 7.6, 1 mM CaCl_2 , 5 mM MgCl_2 , 0.5% BSA, 0.1% NaN_3 , 0.5 M NaCl) twice. The 96-well filtration plate was pretreated with 100 μ l/well of 0.5% polyethylenimine (Cat.#P-3143, Sigma) for 2-4 hours at room temperature and washed with the washing buffer twice before use. The non-specific binding was determined by parallel incubation in the presence of 500 nM of non-labeled eotaxin (Cat.#23209, Genzyme Technne). The radioactivities remained on the filter were measured by liquid scintillation counter (TopCountTM, Packard) after an addition of 45 μ l/well of scintillant (Microscint20, Cat.#6013621, Packard). The inhibition percent at each concentration of compound was calculated, and IC₅₀ values were determined from the inhibition curve.
- 15 [Determination of IC₅₀ values of compounds in calcium mobilization assay] (IC₅₀ Ca²⁺)
- (1) cell
- 20 Human CCR3-transformed K562 cells were used. The human CCR3-transformed K562 cells were maintained in RPMI-1640 supplemented with 10% FCS, 55 μ M 2-mercaptoethanol (Cat.#21985-023, Life Technologies), 1 mM sodium pyruvate, 100 units/ml of penicillin G and 100 μ g/ml of streptomycin and 0.4 mg/ml of Geneticin . Before the calcium mobilization
- 25 assay, cells were pretreated with 5 mM sodium butyrate -containing the culture medium (2×10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Calcium mobilization assay

5 Butyrate-pretreated cells were loaded with Fluo-3AM (Cat.#F-1242, Molecular Probes) in loading buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% BSA, 1 mM probenecid Cat.#P-8761 Sigma, 1 μ M Fluo-3AM, 0.01% pluronic F-127 Cat.#P-6866 Molecular Probes) at a cell density of 1×10^7 cells/ml. Then, cells were washed with calcium assay buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% BSA, 1 mM Probenecid Cat.#P-8761 Sigma). The cell suspension (3.3×10^6 cells/ml) was added into 60 μ l/well in the 96-well clear bottom black plate (Cat.#3904, Costar). Compounds, diluted (5-times concentration of the final concentration) with the calcium assay buffer, were added into 20 μ l/well in the plate 10 minutes before assay. Human recombinant eotaxin, diluted with the calcium assay buffer at the concentration of 50 nM (final concentration; 10 nM), was added into in a polypropylene plate (Cat.#3365, Costar). Mobilization of cytoplasmic calcium was measured by FDSS-6000 or FDSS-3000 (Hamamatsu Photonics) over 60 sec after the stimulation with 10 nM eotaxin. The inhibition percent at the each concentration of compound was calculated, and IC₅₀ values were determined from the inhibition curve.

[Determination of IC₅₀ values of compounds in chemotaxis assay]

(1) cell

25 Human CCR3-transformed L1.2 cells were used. Human CCR3-expressing L1.2 stable transformant was established by electroporation, referring to the methods described in J. Exp. Med. 183:2437-2448, 1996. The human CCR3-transformed L1.2 cells were maintained in RPMI-1640 supplemented with 10% FCS, 100 units/ml of penicillin G and 100 μ g/ml of streptomycin, and 0.4 mg/ml of Geneticin. One day before the chemotaxis assay, cells were

pretreated with 5 mM sodium butyrate -containing culture medium (5×10^5 cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Chemotaxis assay

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Butyrate-pretreated cells were suspended in chemotaxis buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% human serum albumin Cat.#A-1887 Sigma) at a cell density of 1.1×10^7 cells /ml. A mixture of 90 μ l of cell suspension and 10 μ l of compound solution diluted with chemotaxis buffer (10-times concentration of the final concentration) were preincubated for 10 minutes at 37°C. The mixture of cells and compounds was added into the upper chamber of the 24-well chemotaxis chamber (Transwell™, Cat.#3421, Costar, pore size;5 μ m). 0.5 ml of 10 nM of human recombinant eotaxin(Cat.#23209, Genzyme Techne) solution, diluted with chemotaxis buffer, was added into the lower chamber of the chemotaxis plate. Then, chemotaxis was performed in CO₂ incubator at 37°C for 4 hours. After 4hrs incubation, migrated cells were counted using FACScan (Becton Dickinson). The inhibition percent at the each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Selectivity test]

25

Selectivity test was done in calcium mobilization assay and in receptor binding assay by using CCR1, CCR2, CCR4, CCR5, CCR7, CCR8, CXCR1 and PAR-1 (peptidase activate receptor) stable transformants. Methods for the test are the same as that of CCR3. Only the difference is that different stable transformants were used for these selectivity tests.

[Determination of IC50 values of compounds in chemotaxis assay with the use of human eosinophils]

- Human eosinophils were purified from peripheral blood. Twenty five ml of
5 heparinized blood was layered on 15 ml of Mono-Poly Resolving Medium (#16-980-49DN, ICN Biomedicals Co. Ltd, Japan) in 50 ml tube (#2335-050, Iwaki, Japan) gently and then centrifuged at 400G, for 20 min, at room temperature. After centrifugation, red blood cells were removed by hypotonic lysis. The polymorphonuclear leukocyte pellet was incubated with anti-human CD16 Microbeads (#130-045-701,
10 Milteynyi Biotec GmbH, Germany) for 30 min at 4°C. After washing the cells, magnetically labeled neutrophils were then depleted by applying the cell suspension to BS columns (#130-041-304, Milteynyi Biotec GmbH, Germany) attached to VarioMACS (#130-090-282, Milteynyi Biotec GmbH, Germany).
- 15 Chemotaxis assay with the use of the obtained eosinophils was done by the same protocols as that using CCR3 stable transformants, L1.2 cells.

[Primate Chronic Asthma Model: Protocol]

- 20 Materials and Methods: The animals used in this study were wild caught, adult male cynomolgus monkeys (*Macaca fascicularis*) weighing 4.0 to 9.0 kg (Charles River BRF, Inc.). All animals studied demonstrated a naturally occurring respiratory sensitivity to inhaled *Ascaris suum* extract. Animals were housed individually in environmentally controlled rooms in open mesh cages and provided food twice daily
25 and water *ad libitum*. Each animal was fasted for approximately 12 hours prior to the day of study. For each study the animals were anesthetized with ketamine hydrochloride (7mg/kg, i.m.; Ketaset, Fort Dodge, IA) and xylazine (1.2mg/kg, i.m.; Bayer Corp., Elkart, IN), incubated with a cuffed endotracheal tube (5.0 mm ID; Mallinckrodt Critical Care, Glen Falls, NY) and seated in a specially designed support chair. Ketamine (5 mg/kg, i.m.) was used to supplement anesthesia as
30 needed.

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5 Study Protocol: Airway responsiveness (AR) to inhaled methacholine followed by bronchoalveolar lavage (BAL) to assess airway cellular composition (ACC) were determined 3 days before (day 0) and 3 days after (day 10) three alternate-day (days 3,5,7) inhalations of *Ascaris suum* extract. Animals were rested 6 to 8 weeks between studies to allow airway responsiveness and inflammation to return to baseline (pre-antigen) levels. Treatment studies were bracketed by vehicle control studies to assure that no changes in sensitivity to antigen occurred over time.

10 The test compounds dissolved in Ethanol:PEG400:Water (10:50:40 v/v) were administered under light anaesthesia.

15 Aerosol Delivery System and Inhalation Challenges: Aerosol inhalation challenges were administered by intermittent positive pressure breathing with a Bird Mark 7A respirator and micronebulizer (model 8158). Each challenge consisted of 30 breaths (maximum inspiratory pressure=20 cmH₂O). *Ascaris suum* extract (Greer Laboratories, Lenoir, NC) was diluted with PBS to a final threshold concentration previously determined for each animal and administered as an aerosol (particle size <2 µm). Methacholine (Sigma Chemical Co, St. Louis, Missouri) was dissolved in
20 PBS at a concentration of 100 mg/ml and serial dilutions of 30, 10, 3, 1, 0.3 and 0.1 mg/ml were subsequently prepared for nebulization.

25 Measurement of Respiratory System Resistance (Rrs): The animal was connected to a Harvard Ventilator (Harvard Apparatus, S. Natick, MA) via the endotracheal tube and ventilated at a rate between 30-35 breaths per minute. Airflow was measured by
30 a Fleisch (Hans Rudolph) pneumotachograph and thoracic pressure was measured by a validyne pressure transducer (as the difference between the pressure at the distal end of the endotracheal tube and room pressure). The pneumotachograph and validyne were connected to a pre-amplifier and then into an MI² respiratory analyzer (Malvern, PA). Using the primary signals of flow and pressure the analyzer

computed airway resistance and compliance (as well as a number of other respiratory parameters).

5 Methacholine Dose Response Determinations: To assess airway responsiveness to inhaled methacholine, cumulative dose response curves were constructed by administering increasing concentrations of methacholine until increases in Rrs of between 100 and 200% were obtained. A vehicle control challenge was performed prior to the first dose of methacholine. Changes in Rrs were measured continuously over a 10 minute period post aerosol challenge. Aerosol challenges were separated
10 by 5 to 10 minutes or until Rrs returned to baseline values.

15 Determination of PC₁₀₀ Values: The resistance obtained with PBS was set as zero. The percentage increase in resistance above zero at each dose of methacholine was entered into the computer and the program used an algorithm to determine the exact methacholine concentration which caused an increase in resistance of 100% above baseline (PC₁₀₀). Differences (day 10-day 0) in PC₁₀₀ values were calculated as logs (base 10) to normalize the data and account for the large variation in absolute values for the PC₁₀₀ between animals.

20 Bronchoalveolar Lavage: Following methacholine dose response determinations each monkey was placed in the supine position and a fiberoptic bronchoscope (Olympus Optical, model 3C-10, Lake Success, NY) was guided past the carina and wedged into a fifth to seventh generation bronchus. A total of 15 ml of bicarbonate buffered saline (pH 7.4) was infused and gently aspirated through a channel in the
25 bronchoscope. Collected samples were immediately centrifuged at 2000 rpm for 10 minutes at 4°C. The resulting pellets were resuspended in Ca⁺⁺ and Mg⁺⁺ free Hank's balanced salt solution. To avoid possible effects of the BAL procedure on lung cellular composition, BAL was performed on alternating right and left lungs. Total white cells per milliliter of BAL fluid was obtained using a Coulter counter
30 (Coulter Corp., Miami, FL). BAL cell composition was determined by counting a minimum of 200 cells from a Wright's stained cytopsin slide preparation.

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Blood Samples: Blood samples were collected prior to and 30minutes, 1hr and 2hr after the first dose of the test compounds (morning of day 2), immediately before each subsequent dose, and 30 minutes, 1hr and 2hr after the final dose (evening of day 9). Blood was collected from the femoral vein into EDTA, centrifuged at 1500 rpm for 15minutes at 4°C and the plasma stored at -70°C until assayed for the test compounds.

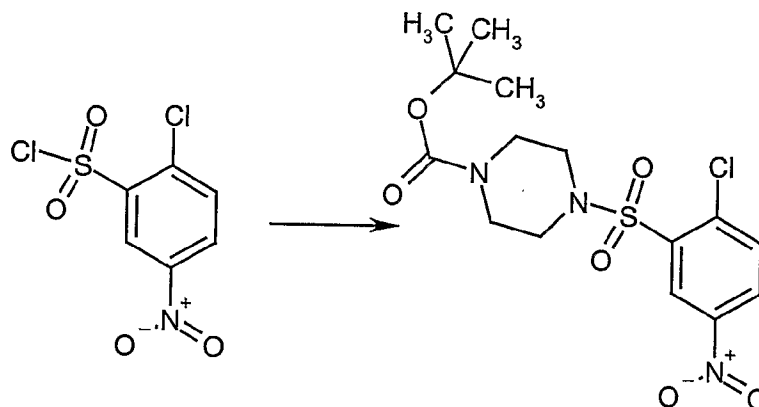
Statistical Analysis: All data were evaluated statistically with the use of students t-test where a p value <0.05 was considered statistically significant.

Results of receptor binding assay (RBA), Ca²⁺ mobilization assay (Ca²⁺) are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in three classes of activity as follows:

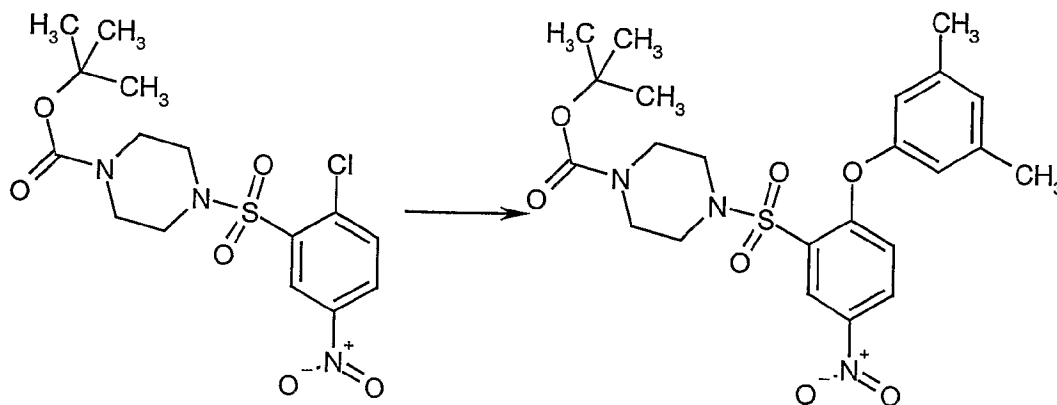
$$IC_{50} = A \text{ } 1\mu\text{M} < B \text{ } 10 \mu\text{M} < C$$

The compounds of the present invention also show more than 100-fold selectivity against CCR1, CCR5, CCR7, CCR8 and CXCR1 in receptor binding assays.

The compounds of the present invention show dose-dependent inhibitory effect on eotaxin-induced chemotaxis of human eosinophils and strong activity in vivo assays.

Example 1-1

- 5 (1) To the solution of 2-chloro-5-nitrobenzenesulfonyl chloride (3.84 g, 15 mmol) in dry THF (30 ml) was added dropwise the mixture of Boc-piperazine (3.07 g, 16.5 mmol) and N, N-diisopropylethylamine (2.33 g, 18 mmol) in dry THF (10 ml) at 0°C with stirring. The mixture was then stirred at room temperature for 3 hrs. The solvent was evaporated and CH₂Cl₂ was added to the residue. The mixture was washed with 0.5 N aqueous HCl, brine, saturated aqueous NaHCO₃, brine, successively, dried over MgSO₄.
10 The solvent was evaporated to give *tert*-butyl 4-[(2-chloro-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate as white powder (5.80g, 95.3%).



- 15 (2) To the solution of 3,5-dimethylphenol (1.92 g, 15.72 mmol) in DMF (50 ml) was added NaH (60%, 0.629g, 15.72 mmol) at 0°C with stirring. *tert*-Butyl 4-[(2-

- 64 -

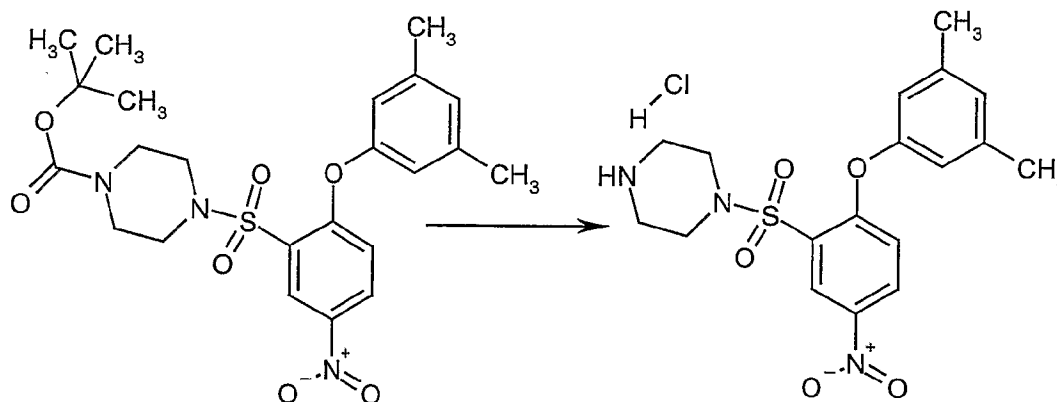
chloro-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (5.80 g, 14.29 mmol) was added to the mixture after 30 min. The mixture was stirred at room temperature for 2 hrs. 100 ml of ice water was added, the precipitate was collected by filtration, washed with water and dried *in vacuo* to give *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-1-piperazinecarboxylate as white powder (6.90 g, 98.2%): mp 232-233°C; ¹H NMR (500 MHz, CDCl₃) 1.45 (9H, s), 2.35 (6H, s), 3.35 (4H, t, J = 5 Hz), 3.51 (4H, t, J = 5 Hz), 6.72 (2H, s), 6.91-6.95 (2H, m), 8.26 (1H, t), 8.86 (1H, s); HPLC-MS (ESI): Calcd for C₂₃H₂₉N₃O₇S [M + H]⁺ 492, Found: 492.

Molecular weight: 491.5675

Activity grade RBA: C

Activity grade Ca²⁺: C

Example 1-2



- (1) To the suspension of *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-1-piperazinecarboxylate (620 mg, 1.26 mmol) which was prepared in the Example 1-1 in CH₂Cl₂ (3ml) was added trifluoroacetic acid (2 ml) at 0°C, the mixture was stirred at 0°C for 3 hrs. The solvent was evaporated *in vacuo* and 20 ml of toluene was added, the solvent was evaporated *in vacuo* again. To the residue was added CH₂Cl₂ (15 ml), and the mixture was cooled

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5 to 0°C. 4 N HCl solution in 1,4-dioxane (2 ml) was added and the mixture was stirred for 15 min at 0°C. The solvent was evaporated, and diethyl ether (5 ml) was added to the residue. The precipitate was collected by filtration and dried to give 1- $\{[2-(3,5\text{-dimethylphenoxy})\text{-}5\text{-nitrophenyl}]\text{sulfonyl}\}$ piperazine hydrochloride

10 (480 mg, 88.9%): mp 264-266°C; ^1H NMR (300 MHz, DMSO-*d*₆) δ 2.33 (6H, s), 3.18 (4H, br), 3.56 (4H, br), 6.96 (2H, s), 7.03-7.05 (2H, m), 8.45 (1H, q, $J = 9.2$ Hz), 8.60 (H, d, $J = 2.8$ Hz), 9.38 (2H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₁N₃O₅S $[M + H]^+$ 392, Found: 392.

Molecular weight: 427.9101

Activity grade RBA: A

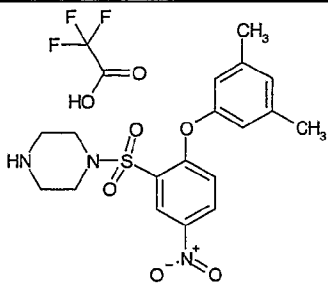
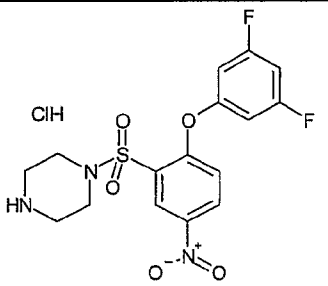
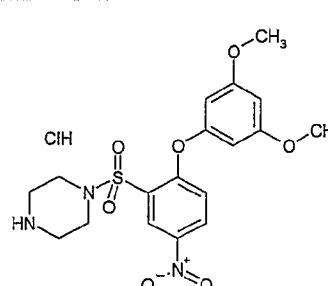
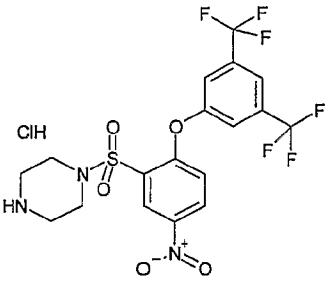
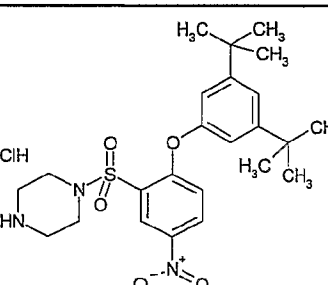
Activity grade Ca²⁺: A

15

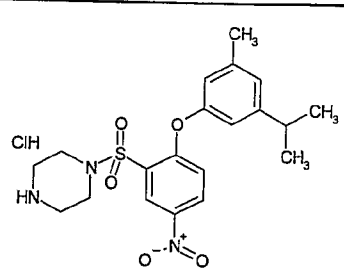
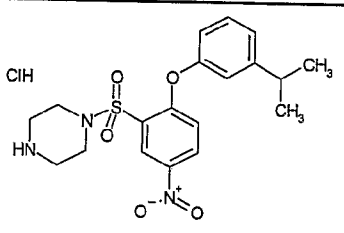
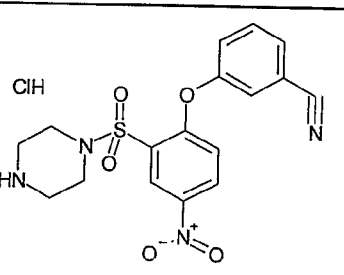
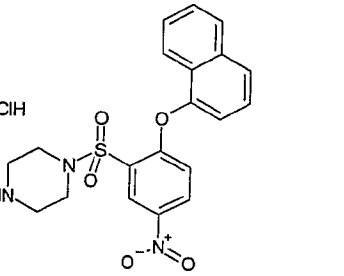
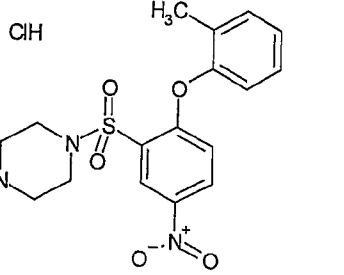
In the similar manner as described in Example 1-1 or 1-2 above, compounds in Example 1-3 to 1-100 as shown in Table 1 were synthesized.

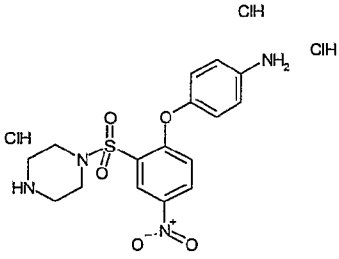
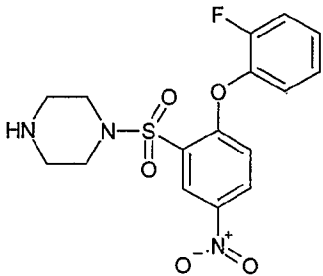
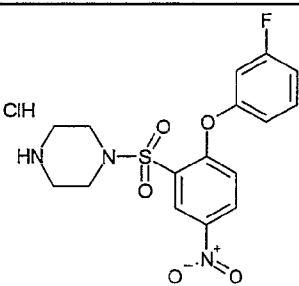
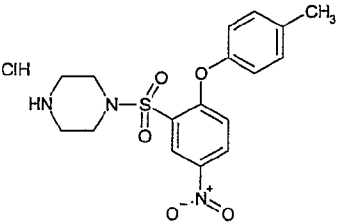
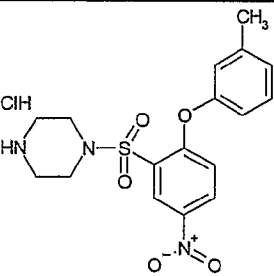
- 66 -

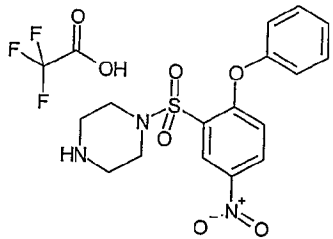
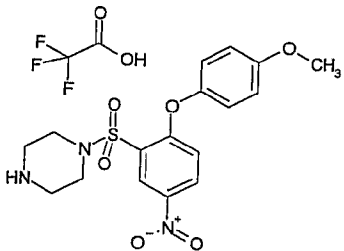
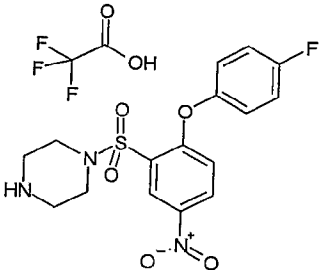
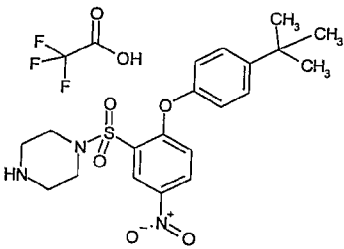
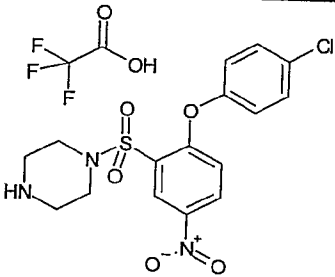
Table 1

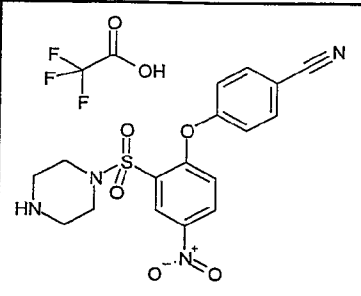
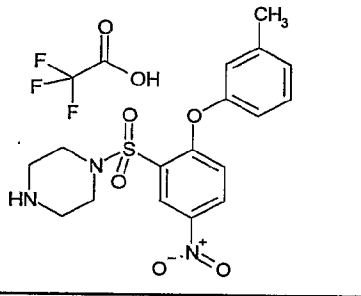
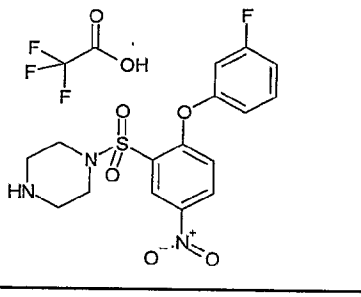
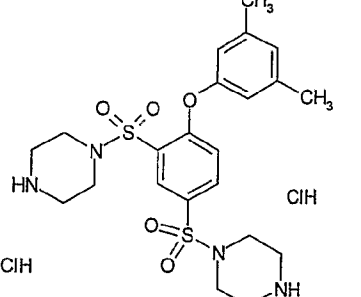
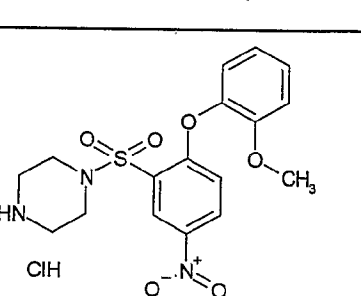
EX.No	molstructure	MW	M+1	mp	RBA	Ca2+
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1-4		435.83682	400	273-274	A	A
1-5		459.90894	424	211-213	C	C
1-6		535.85272	500	188-191	A	A
1-7		512.07268	476	141-143	C	C

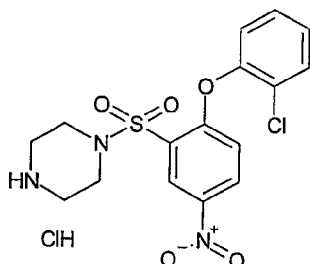
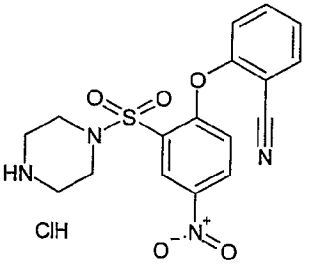
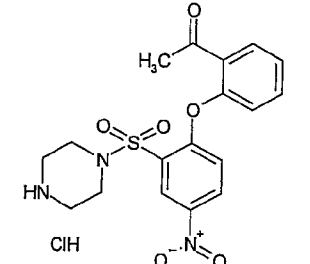
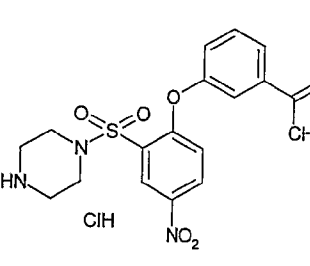
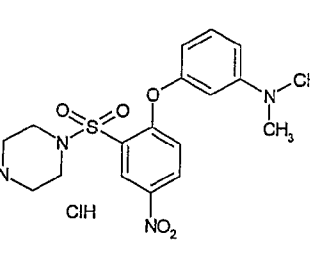
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1-8		455.96432	420	182-185	A	A
1-9		441.93723	406	168-170	A	A
1-10		424.86584	389	265-267	B	B
1-11		449.9165	414	196-198	B	A
1-12		413.88305	378	167-169	B	B

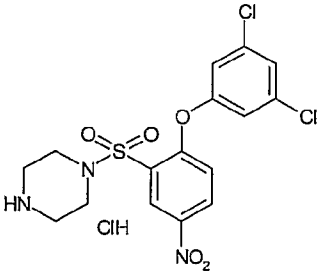
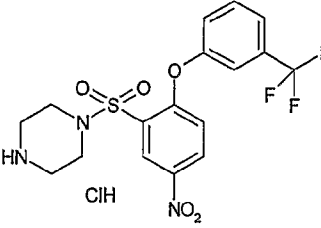
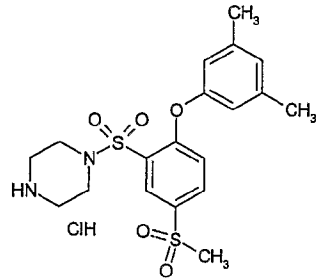
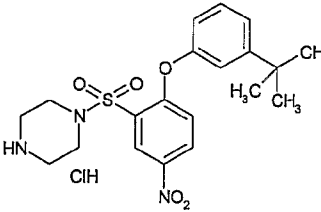
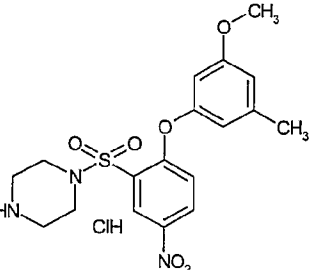
1-13		487.79257	379	246-248	C	C
1-14		381.38542	382	118-120	B	
1-15		417.84639	382	227-229	B	
1-16		413.88305	378	188-192	C	
1-17		413.88305	378	242-244	A	

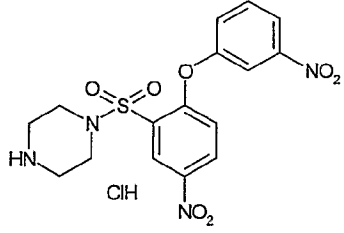
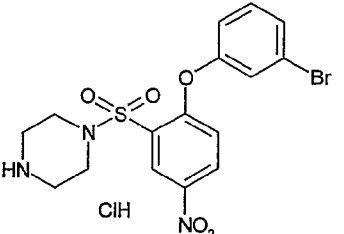
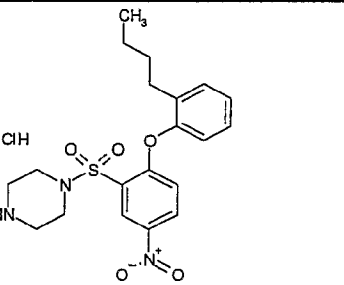
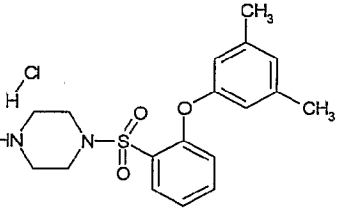
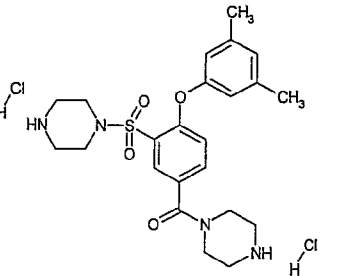
1-18		477.41926	363		B	B
1-19		507.44575	394		C	C
1-20		495.40969	382		C	C
1-21		533.52762	420		C	C
1-22		511.86429	398		C	C

1-23		502.42914				
1-24		491.44635	378		A	A
1-25		495.40969	382		A	A
1-26		567.55814	495	214-220		
1-27		429.88245	394	142	A	A

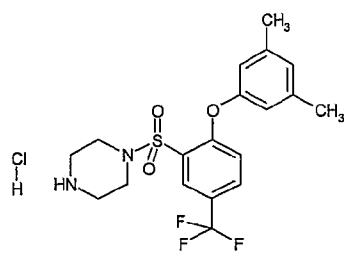
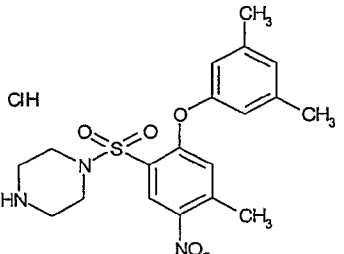
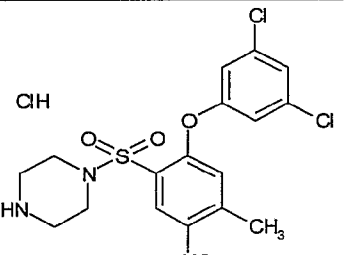
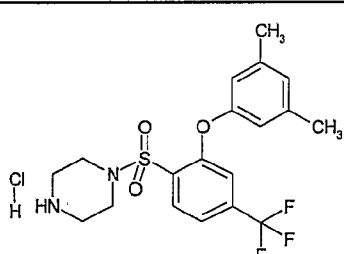
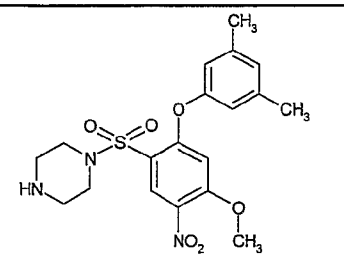
1-28	 ClH	434.30099	398	166-169	B	A
1-29	 ClH	424.86584	389	133	B	B
1-30	 ClH	441.8936	406	194-200	C	C
1-31	 ClH	441.8936	406	77	C	C
1-32	 ClH	442.92481	407	182	C	B

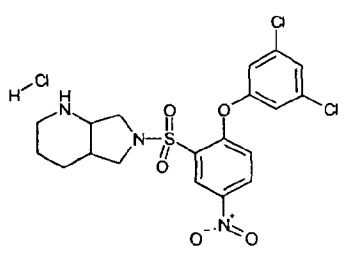
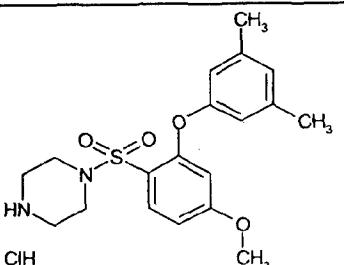
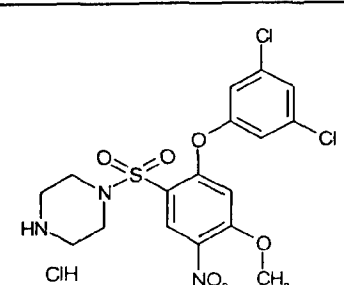
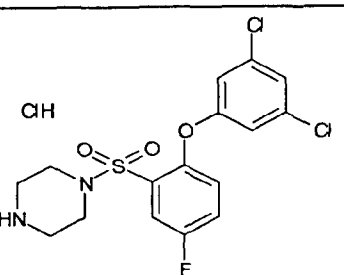
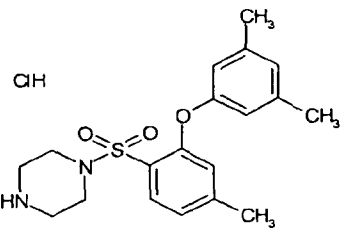
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1-33		468.74602	432	260-264	A	A
1-34		467.85434	432	128	A	A
1-35		461.0025	425	267-268	B	A
1-36		455.96432	420	155	B	A
1-37		443.90954	408	113	A	A

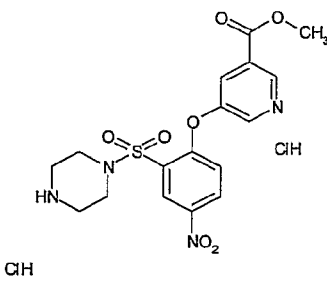
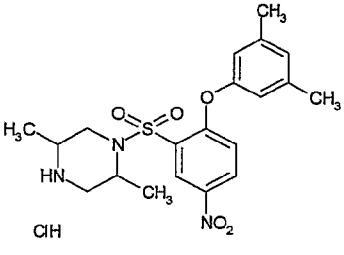
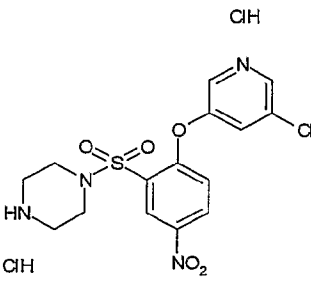
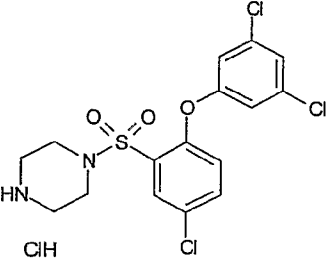
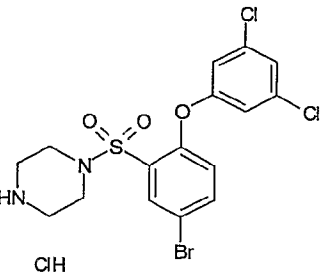
1-38		444.85349	409	150	B	A
1-39		478.75199	442	119	A	A
1-40		455.96432	420	140-150	A	A
1-41		382.91261	347	205-207	C	B
1-42		531.50589	459	288-290	C	C

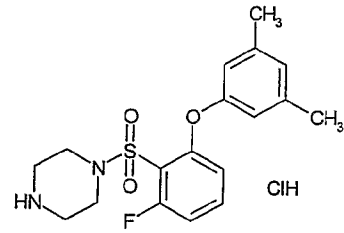
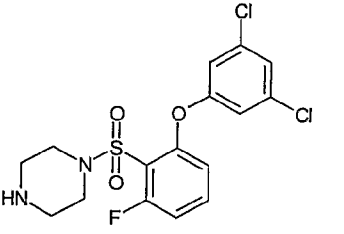
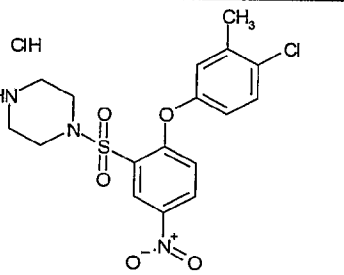
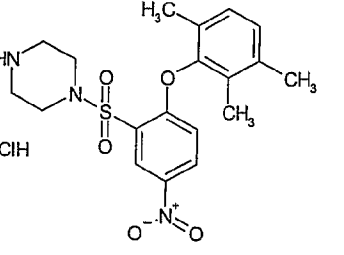
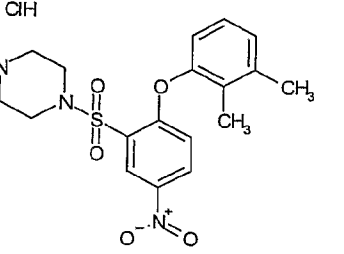
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1-43		450.91099	415	238-239	A	A
1-44		441.93723	406	159	B	B
1-45		482.77311	446	168	A	A
1-46		450.91099	415	250-251	C	C
1-47		457.93663	422	188	B	C

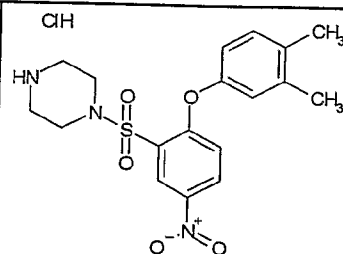
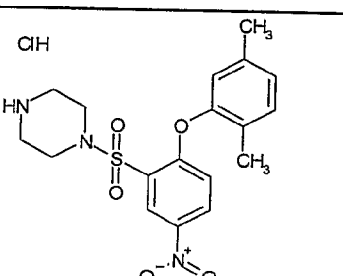
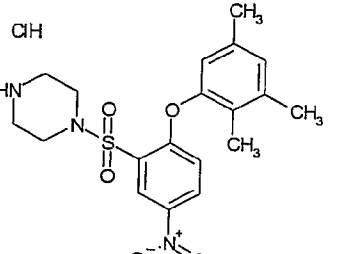
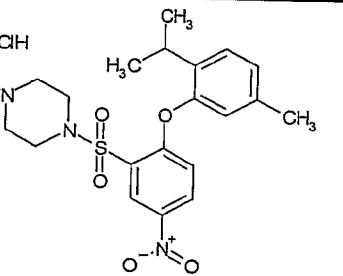
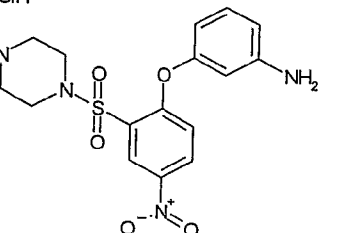
1-48		508.81135	471	170	A	A
1-49		412.9391	377	125		A
1-50		498.77251	462	181		A
1-51		441.73892	405	145	A	A
1-52		396.9397	361	136		A

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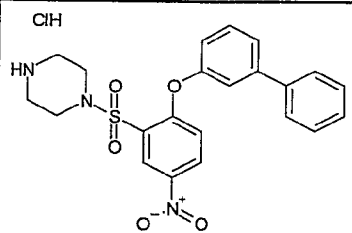
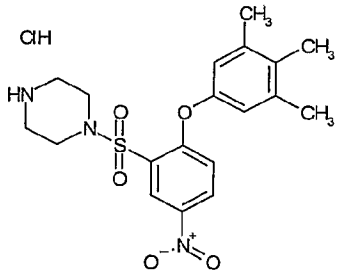
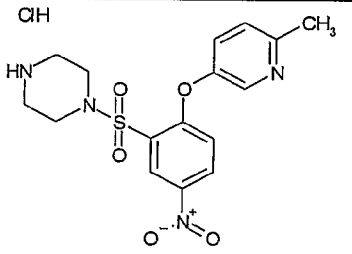
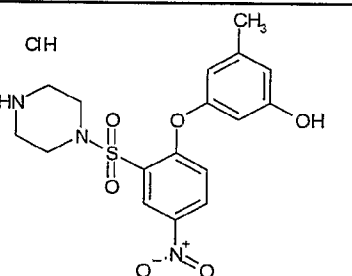
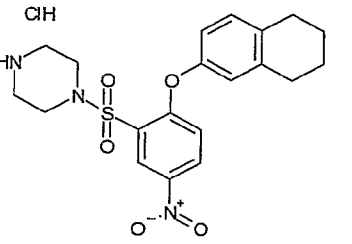
1-53		495.34155	423	amorphous		B
1-54		455.96432	420	159	A	A
1-55		471.74954	n.d.	231		A
1-56		458.19352	421	255-257	A	A
1-57		502.64452	467	269-271	A	A

1-58		400.90304	365	204		A
1-59		441.73892	405	306		A
1-60		448.32808	412	204	B	B
1-61		441.93723	406	220	B	B
1-62		427.91014	392	142	A	A

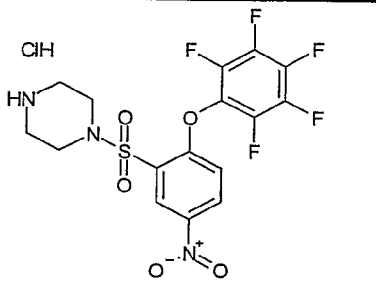
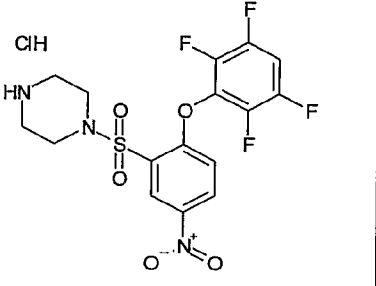
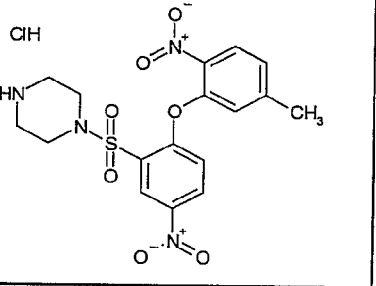
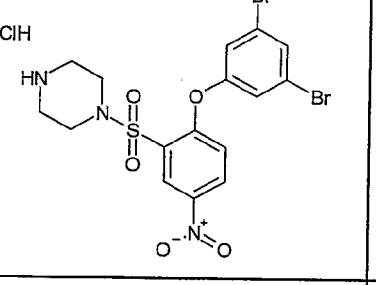
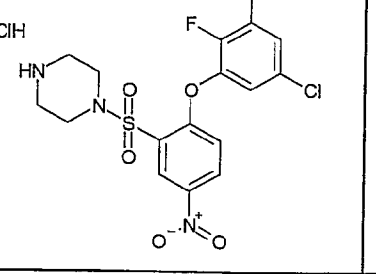
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1-63		427.91014	392	142	B	A
1-64		427.91014	392	141	A	A
1-65		441.93723	406	187	A	A
1-66		455.96432	420	193	B	B
1-67		414.87063	379	248		A

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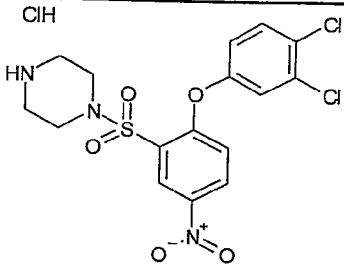
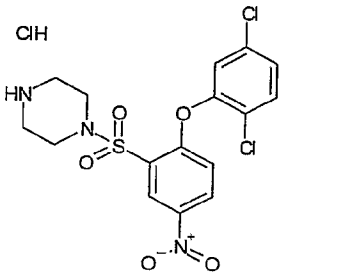
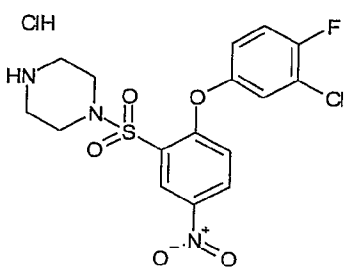
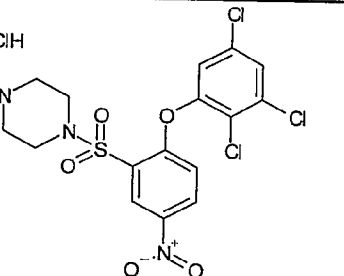
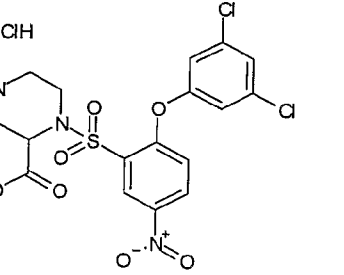
1-68		475.95474	440	99		A
1-69		441.93723	406	248		A
1-70		414.87063	379	237		A
1-71		429.88245	394	182		A
1-72		453.94838	418	168		A

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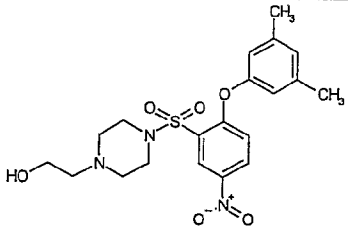
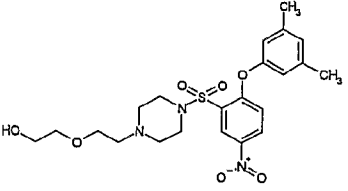
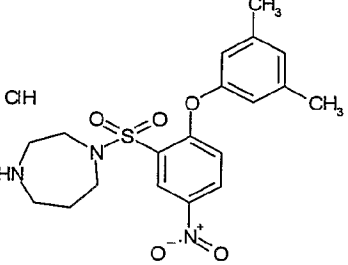
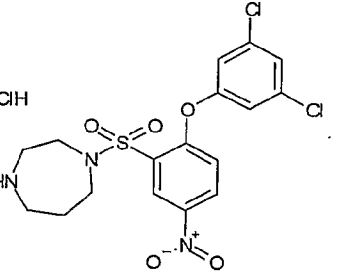
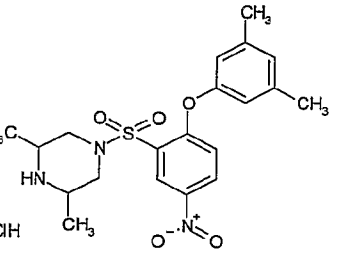
1-73		489.80811	454	297		A
1-74		471.81768	436	104	A	A
1-75		458.88058	423	215		A
1-76		557.64802	521	205	A	A
1-77		486.73645	450	263	A	A

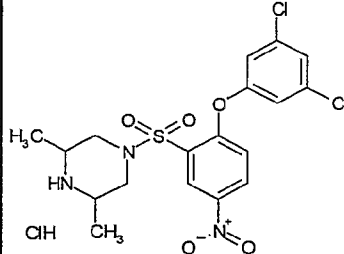
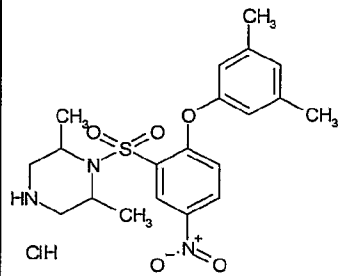
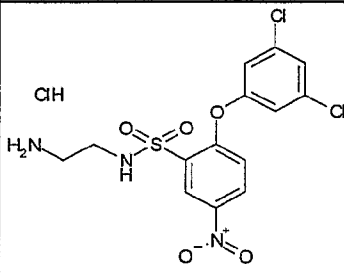
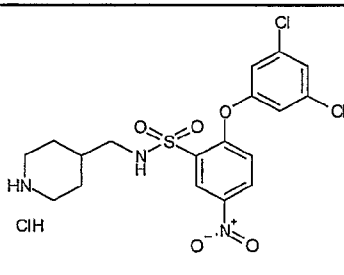
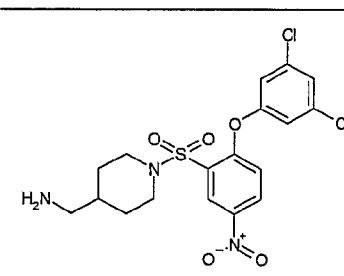
1-78		482.77311	445	>300		A
1-79		462.35517	427	178-179	A	A
1-80		448.32808	413	166-167	A	A
1-81		490.40935	455		C	C
1-82		468.74602	433	173-174	B	

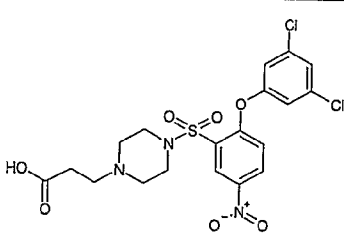
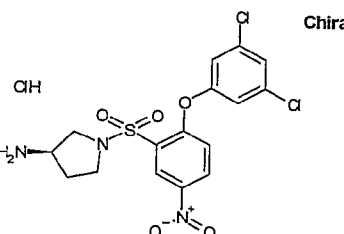
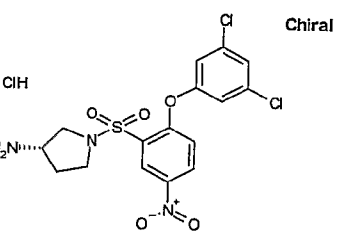
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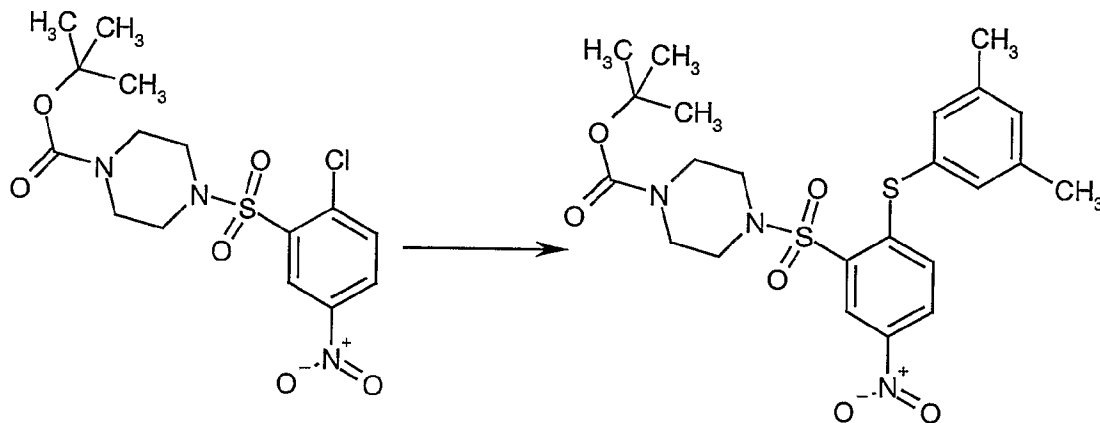
1-83		468.74602	433	167-168	C	
1-84		468.74602	433	179-180	A	A
1-85		452.29142	417	172-173		
1-86		503.19105	468	188-189	A	A
1-87		512.75597	475	240-241	A	A

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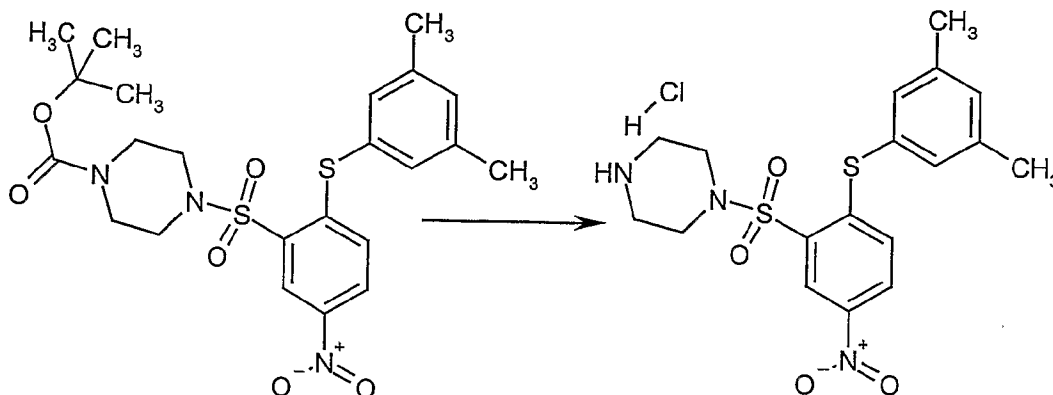
1-88		435.50275	436	163-164	A	A
1-89		479.55633	480		A	A
1-90		441.93723	406		A	A
1-91		482.77311	446	261-263	A	A
1-92		455.96432	420		A	A

1-93		496.8002	460		A	A
1-94		455.96432	420	>300		A
1-95		442.70778	446	220-221		A
1-96		496.8002				A
1-97		460.33923	460	148-151		A

1-98	 <chem>O=C(O)CCN1CCN(C1)S(=O)(=O)c2ccc([N+](=O)[O-])cc2Oc3cc(Cl)cc(Cl)c3</chem>	504.34918	504	200-201		A
1-99	 <chem>ClH[N+]([O-])=Oc1ccc(OC2=CC(=CC=C2C3=CC(=CC=C3)C(Cl)=CC(Cl)=C3)OC4=CC=CC=C4S(=O)(=O)N5C[C@H](C[C@@H](C5)N)C(=O)O)cc1</chem> Chiral	468.74602	432	247-250		A
1-100	 <chem>ClH[N+]([O-])=Oc1ccc(OC2=CC(=CC=C2C3=CC(=CC=C3)C(Cl)=CC(Cl)=C3)OC4=CC=CC=C4S(=O)(=O)N5C[C@@H](C[C@H](C5)N)C(=O)O)cc1</chem> Chiral	468.74602	432	256-258	A	A

Example 2-1

- 5 (1) To the solution of 3,5-dimethylthiophenol (82.94 mg, 0.60 mmol) in dry THF (5ml) was added NaH (60%, 24 mg, 0.60 mmol). *tert*-Butyl 4-[(2-chloro-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (162mg, 0.4 mmol), which was prepared in the step(1) of Example 1-1, was added to the solution after 10min. The resulting mixture was stirred at room temperature overnight. 60 mg of
- 10 K_2CO_3 was added and the mixture was stirred at room temperature for 6hrs. EtOAc was added and the mixture was washed by 10% aqueous Na_2CO_3 , brine, successively. The organic layer was dried over $MgSO_4$. The solvent was evaporated to 3 ml, the produced white crystal was collected by filtration and dried to give *tert*-butyl 4-({2-[(3,5-dimethylphenyl)sulfanyl]-5-nitrophenyl}-sulfonyl)-1-piperazinecarboxylate (148 mg , 72.9%).
- 15



- 87 -

- (2) To the solution of *tert*-butyl 4-({2-[(3,5-dimethylphenyl)sulfanyl]-5-nitrophenyl}sulfonyl)-1-piperazinecarboxylate (100 mg, 0.20 mmol) in dry CH₂Cl₂ (3 ml) was added 4 N HCl (0.5 ml) solution in 1,4-dioxane, the mixture was stirred overnight at room temperature. The solvent was evaporated, and 5ml of diethyl ether was added to the residue. The precipitate was collected by filtration and dried to give 1-({2-[(3,5-dimethylphenyl)sulfanyl]-5-nitrophenyl}sulfonyl)piperazine hydrochloride (82 mg, 93.8%): mp 225-227°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.34 (6H, s), 3.18 (4H, br), 3.63 (4H, br), 7.09 (1H, d, J = 9Hz), 7.25 (1H, s), 7.31 (2H, s), 8.30 (1H, q, J = 9 Hz), 8.54 (1H, d, J = 2), 9.57 (2H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₁N₃O₄S₂ [M + H]⁺ 408, Found: 408.

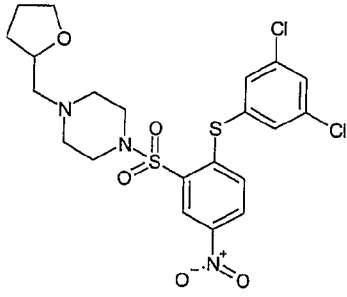
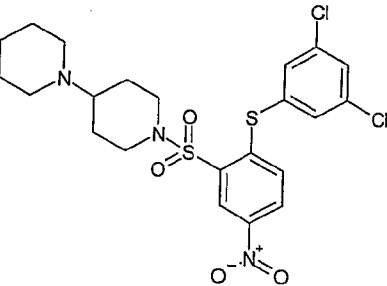
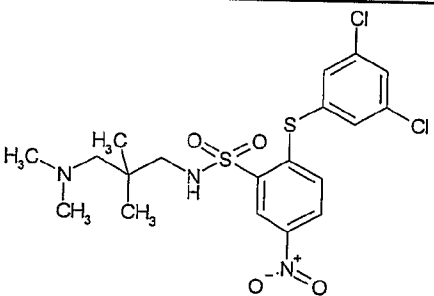
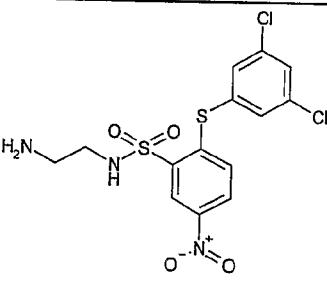
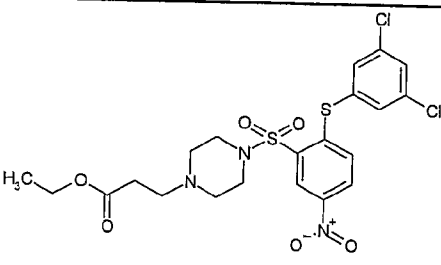
Molecular weight: 443.9747

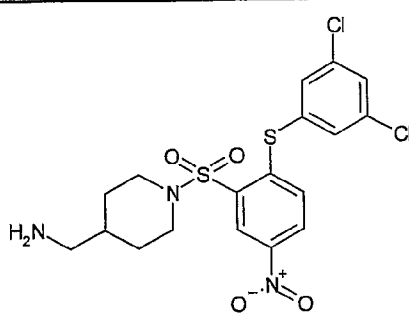
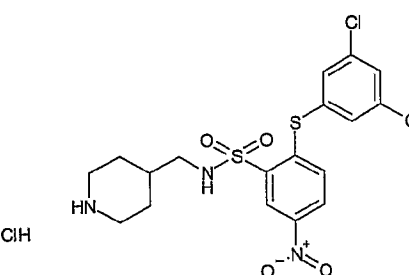
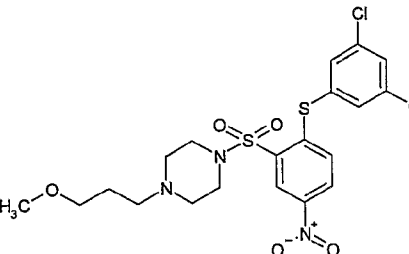
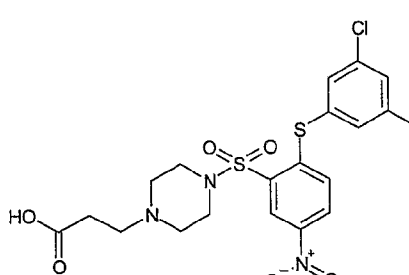
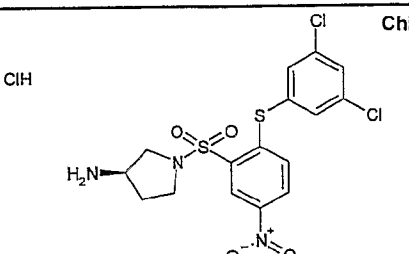
Activity grade RBA: A

15 Activity grade Ca²⁺: A

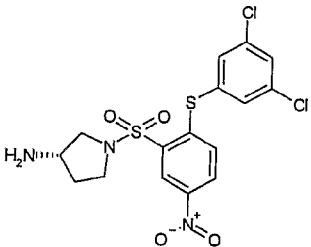
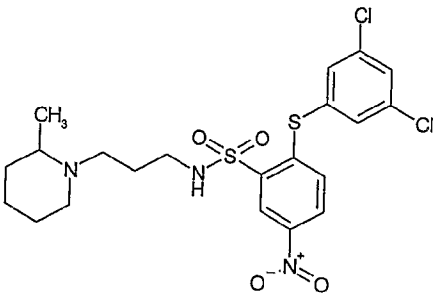
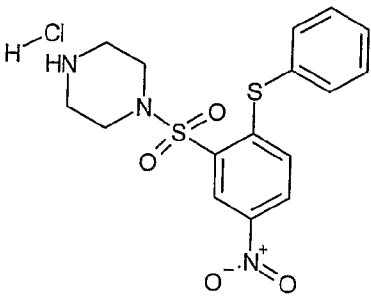
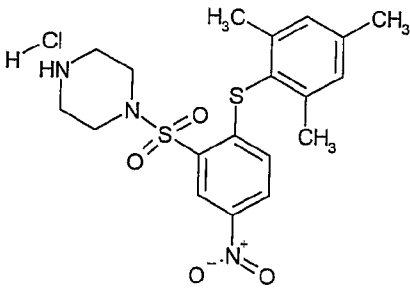
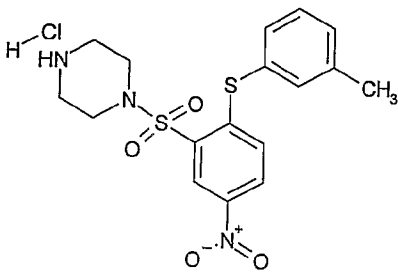
In the similar manner as described in Example 2-1 above, compounds in Example 2-2 to 2-24 as shown in Table 2 were synthesized.

Table 2

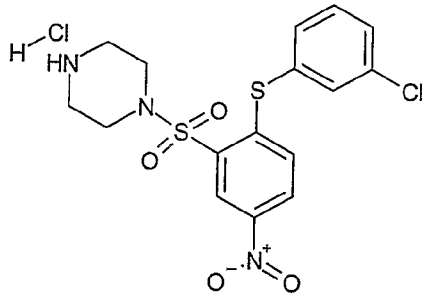
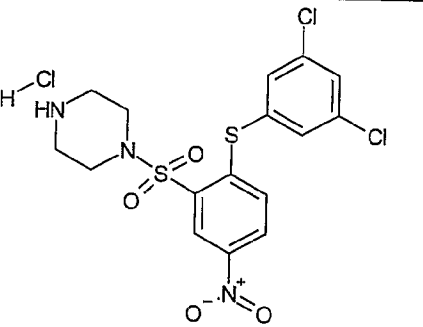
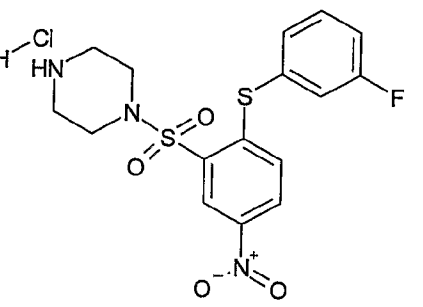
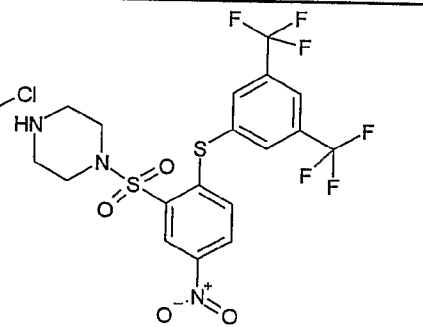
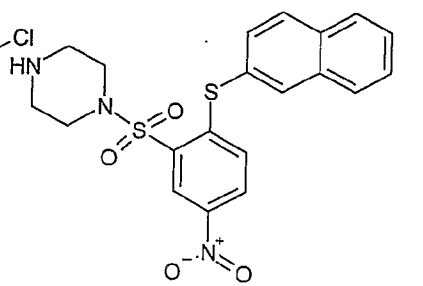
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2-2		532.46856	533	147-148		A
2-3		530.49625	531	191-192	A	A
2-4		492.44686	492,			A
2-5	ClH 	458.77238	421	189		A
2-6		548.46796	548	156-158		A

2-7		476.40383	476	147-149		A
2-8	<p>ClH</p> 	512.8648	476	205-207		A
2-9		520.45741	520	131-133		A
2-10		520.41378	520	209-211		A
2-11	<p>ClH</p> <p>Chiral</p> 	484.81062	448	270	A	A

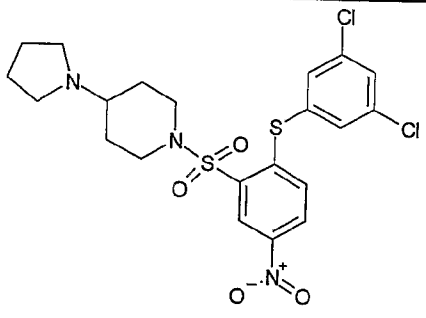
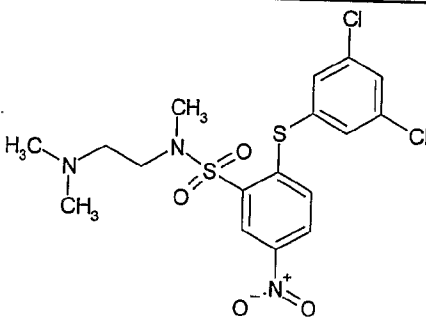
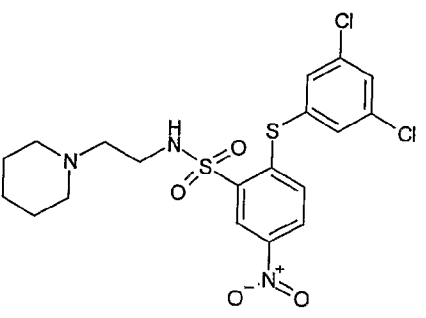
- 90 -

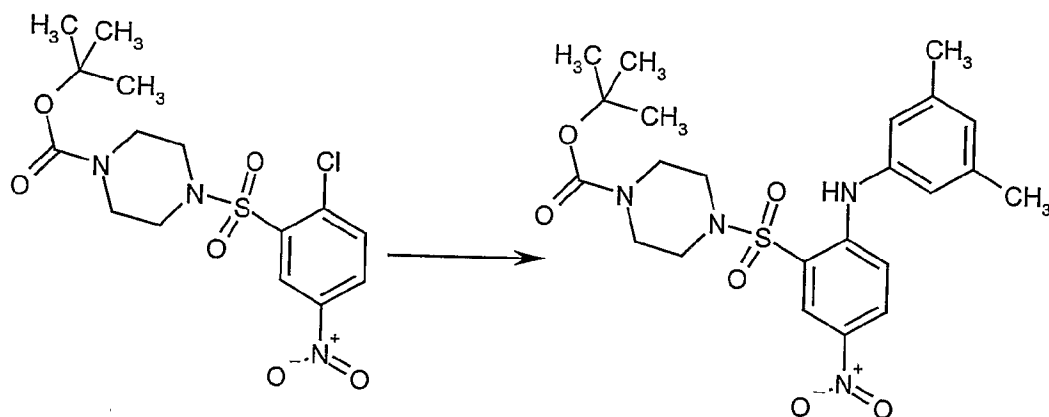
2-12	<p>ClH</p> <p>Chiral</p> 	484.81062	449	263	A	A
2-13		518.4851	518		A	A
2-14		415.92056	380			B
2-15		458.00183	422	274		B
2-16		429.94765	394	229-231		A

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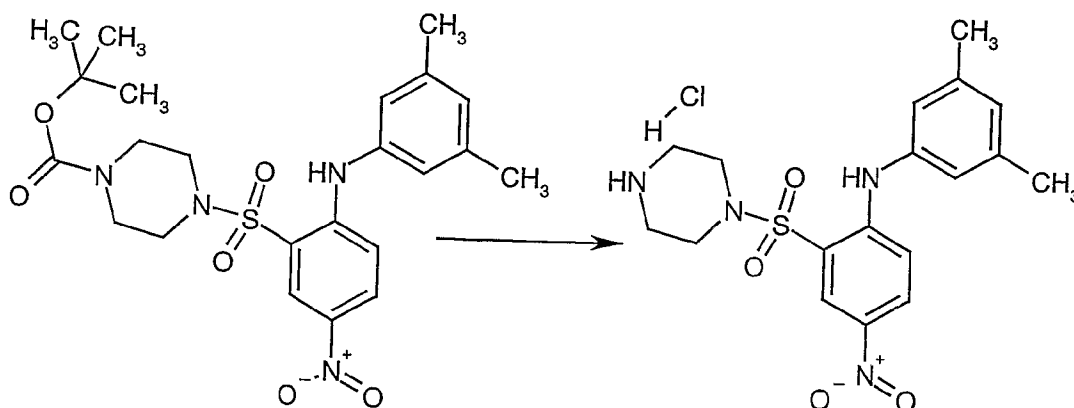
2-17		450.36559	414	235-237		A
2-18		484.81062	448	262-264		A
2-19		433.91099	398	236-238		A
2-20		551.91732	516	230-231		A
2-21		465.9811	430	273		B

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2-22		516.46916	516	213	A	A
2-23		464.39268	464	102	A	A
2-24		490.43092	490		A	A

Example 3-1

- 5 (1) To the solution of 3,5-dimethylaniline (96.9 mg, 0.80 mmol) in dry THF (15 ml) was added NaH (60%, 24 mg, 0.6 mmol) followed by *tert*-butyl 4-[(2-chloro-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (162.3 mg, 0.40 mmol), which was prepared in the step (1) of Example 1-1 and the mixture was stirred at 80°C for 2 hrs. The solvent was evaporated and 15 ml of ice water was added to the residue. The mixture was extracted with CH₂Cl₂. The combined extract was washed with saturated aqueous NaHCO₃, brine, successively, dried over MgSO₄. The solvent was evaporated and 10 ml of diethyl ether was added to the residue, the produced precipitate was collected by filtration and dried to give *tert*-butyl 4-[(2-[(3,5-dimethylphenyl)amino]-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (110 mg, 56.1%).



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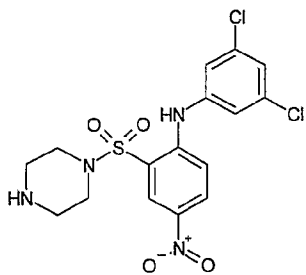
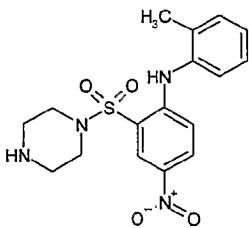
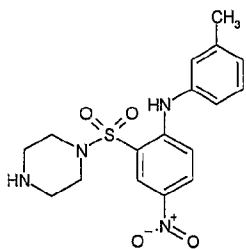
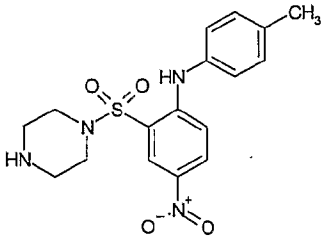
- (2) To the suspension of *tert*-butyl 4-({2-[(3,5-dimethylphenyl)amino]-5-nitro-phenyl}sulfonyl)-1-piperazinecarboxylate (150 mg, 0.31 mmol) in CH₂Cl₂ (2 ml) was added 4N HCl solution in 1,4-dioxane (1ml), the mixture was stirred for 2 hrs at room temperature. The mixture was filtered. The filtrate was evaporated, and 5ml of diethyl ether was added to the residue. The precipitate was collected by filtration and dried to give N-(3,5-dimethyl-phenyl)-4-nitro-2-(1-piperazinylsulfonyl)aniline dihydrochloride (115 mg, 81.2%) : mp 175-179°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.30 (6H, s), 3.18 (4H, t, J = 5.3 Hz), 3.44 (4H, q, J = 5.3 Hz), 6.97 (3H, s), 7.10 (1H, d, J = 9.4 Hz), 8.25 (1H, q, J = 9.4 Hz), 8.34 (1H, d, J = 2.64 Hz), 8.47 (1H, s), 9.23 (2H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₂N₄O₄S [M + H]⁺ 391, Found: 391.

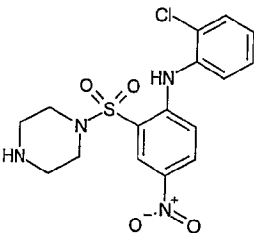
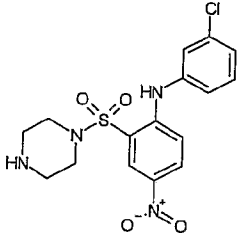
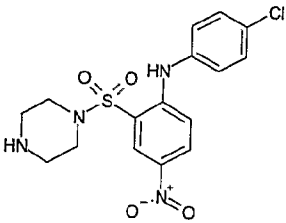
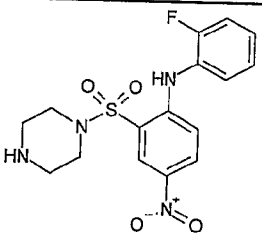
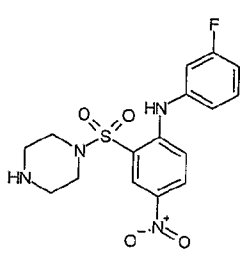
Molecular weight: 463.3864

Activity grade RBA: A

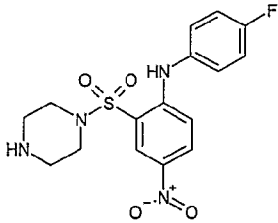
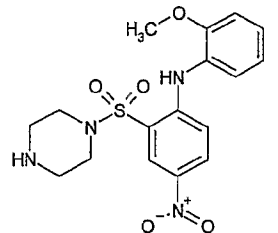
In the similar manner as described in Example 3-1 above, compounds in Example 3-2 to 3-12 as shown in Table 3 were synthesized.

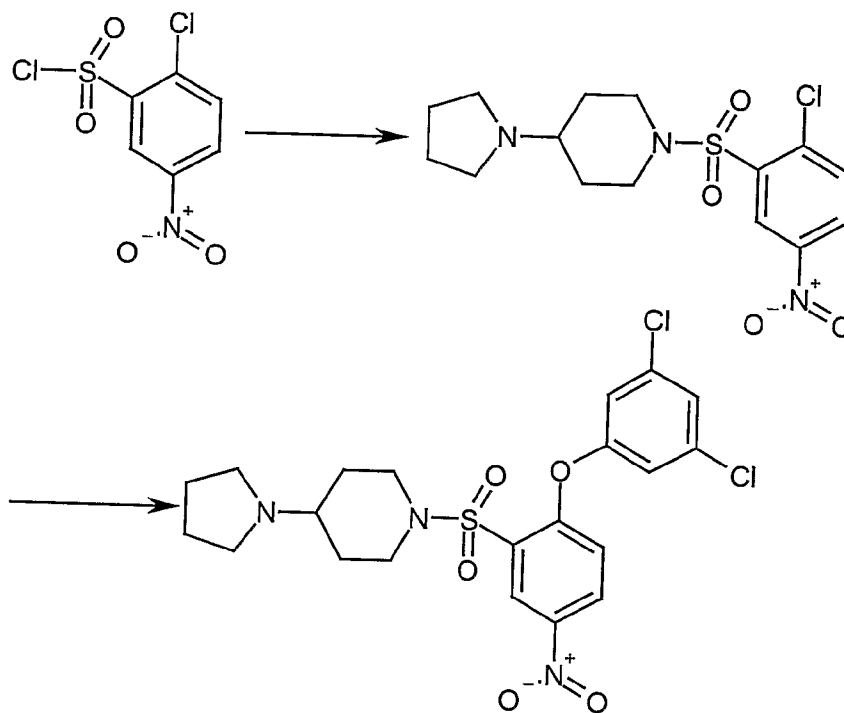
Table 3

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
3-2	ClH 	467.76129	431	160	A	A
3-3	 ClH	412.89832	377	155	B	B
3-4	 ClH	412.89832	377	158	B	B
3-5	 ClH	412.89832	377	239-240	C	B

3-6	 ClH	433.31626	397		C	B
3-7	 ClH	433.31626	397	150		A
3-8	 ClH	433.31626	397	267		A
3-9	 ClH	416.86166	381	275		A
3-10	 ClH	416.86166	381			A

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3-11	 ClH	416.86166	381			A
3-12	 ClH	428.89772	393	241-242		A

Example 4-1

- 5 (1) To the solution of 2-chloro-5-nitrobenzenesulfonyl chloride (2.05g, 8 mmol) in THF (60 ml) was added the solution of 4-(1-pyrrolidinyl)piperidine (1.23 g, 8 mmol) and NEt₃ (0.89g, 8.8 mmol) in THF (15 ml) dropwise. The mixture was stirred at room temperature for 2hrs. 3,5-Dichlorophenol (1.96 g, 12 mmol) was added to the above mixture followed by NaH (60%, 0.96 g, 12 mmol). The resulting mixture was stirred at 65°C for 8 hrs, and cooled to room temperature. The precipitate was collected by filtration and washed with THF, Et₂O, and water, successively, dried *in vacuo* to give 1-{[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-4-(1-pyrrolidinyl)piperidine as white powder (3.2 g, 79.9%): mp 217-218°C; ¹H NMR (500 MHz, CDCl₃) δ 1.26 (2H, s), 1.63 (4H, d, J = 10 Hz), 1.77 (4H, s), 1.92 (2H, d, J = 6.1Hz), 2.15 (1H, m), 2.34 (6H, s), 2.97 (2H, p, J = 10 Hz), 3.86 (2H, q, J = 9.3 Hz), 6.74 (2H, s), 6.90 (1H, d, J = 9.1 Hz), 6.94 (1H, s), 8.24 (1H, q, J = 9.1 Hz), 8.86 (1H, d, J = 2.85 Hz); HPLC-MS (ESI): Calcd for C₂₁H₂₃Cl₂N₃O₅S [M + H]⁺ 501, Found: 500 and 502

- 99 -

Molecular weight: 500.4046

IC₅₀ (CCR3): 8 μM

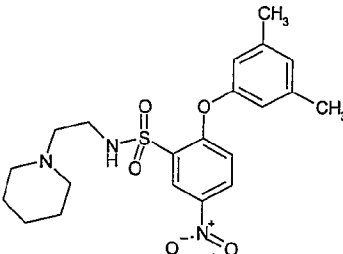
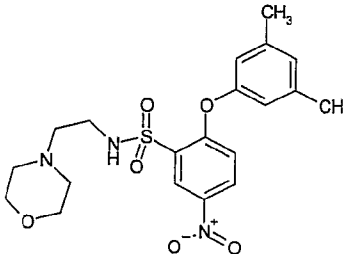
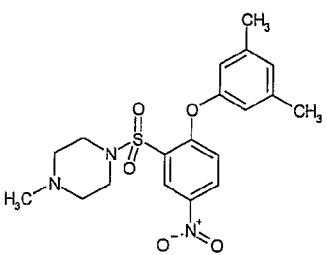
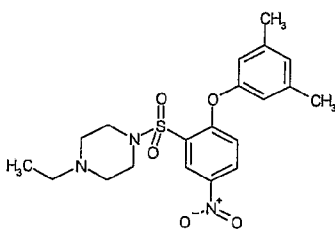
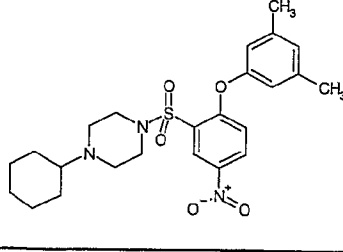
IC₅₀ (Ca²⁺): 7 μM

5 IC₅₀ (Chemotaxis): 5 μM

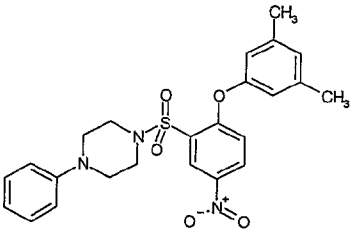
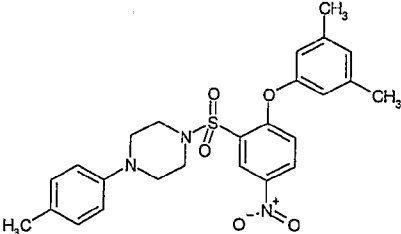
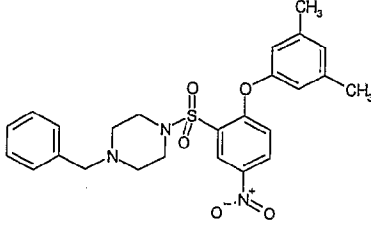
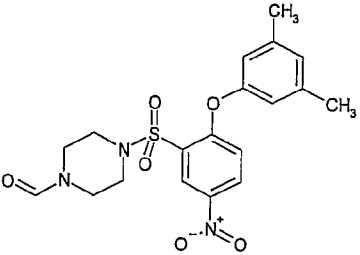
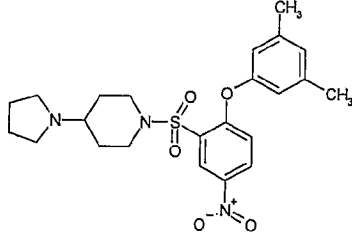
In the similar manner as described in Example 4-1 above, compounds in Example 4-2 to 4-41 as shown in Table 4 were synthesized.

- 100 -

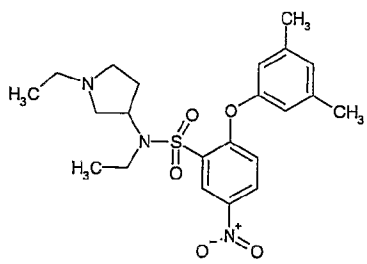
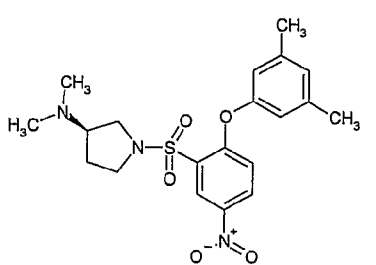
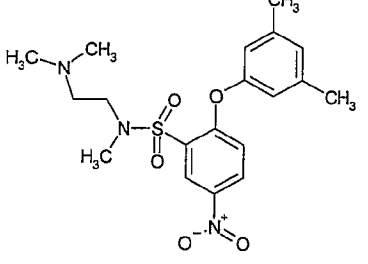
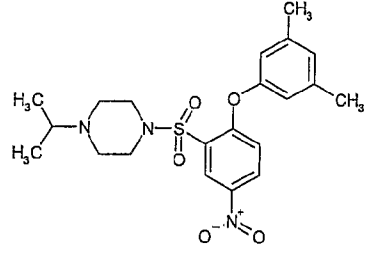
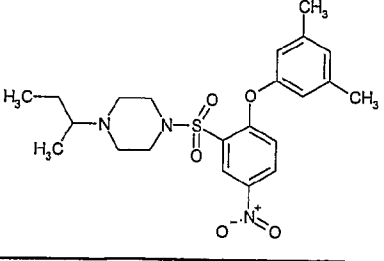
Table 4

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
4-2		433.53044	434		A	A
4-3		435.50275	436		B	A
4-4		405.47626	406	131-132	A	A
4-5		419.50335	420	111-112	A	A
4-6		473.59577	474	190-192	A	A

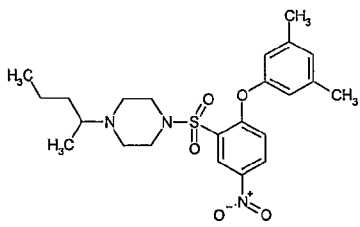
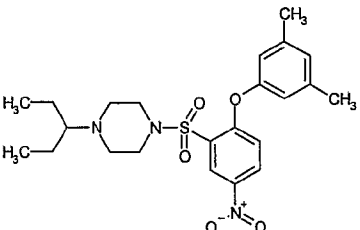
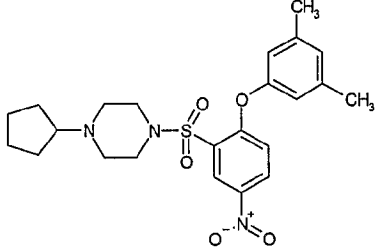
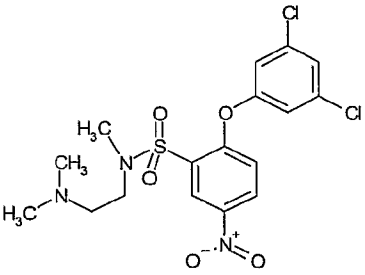
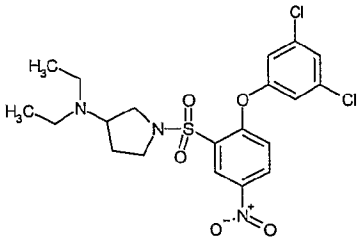
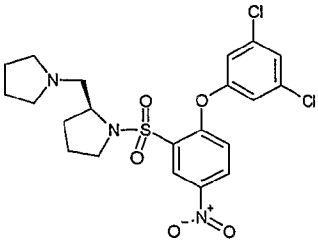
- 101 -

4-7		467.54795	468	168-169	C	C
4-8		481.57504	482	168-170	C	C
4-9		481.57504	482	123-124	C	
4-10		419.45972	437	210-212	C	
4-11		459.56868	460	156-158	A	

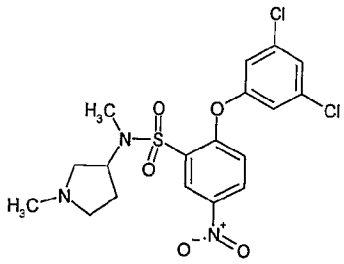
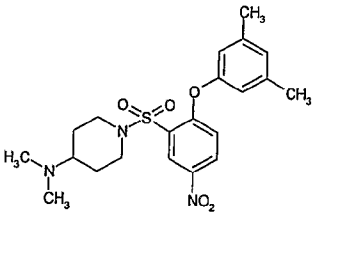
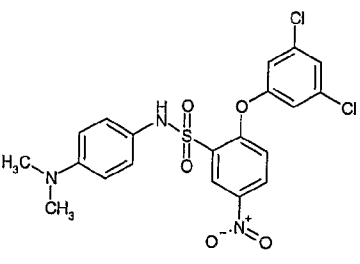
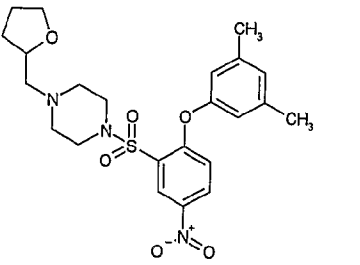
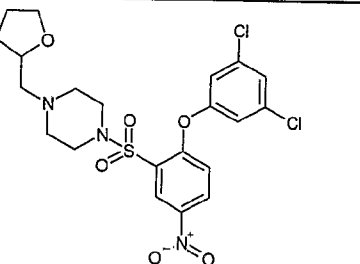
- 102 -

4-12		447.55753	448	86-88	A	A
4-13		419.50335	420	115-116	A	A
4-14		407.4922	408	75-77	A	A
4-15		433.53044	434	129-131	A	A
4-16		447.55753	448	134-135	A	A

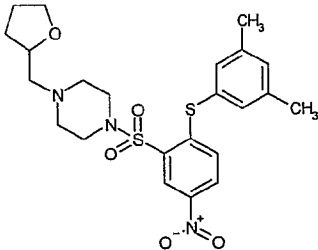
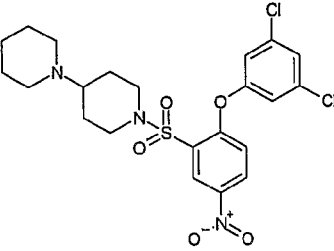
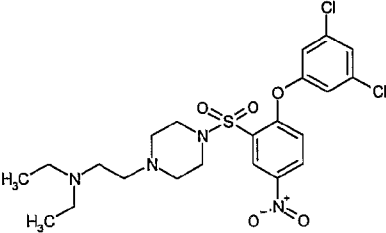
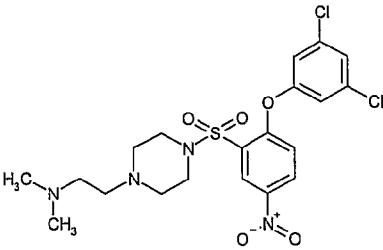
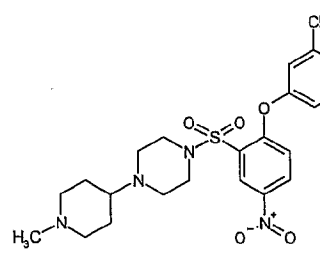
- 103 -

4-17		461.58462	462	93-95	A	A
4-18		461.58462	462	131-132	A	B
4-19		459.56868	460	169-171	A	A
4-20		448.32808	448	105-107	A	A
4-21		488.39341	488	120-121	A	A
4-22		500.40456	500	200-202	A	A

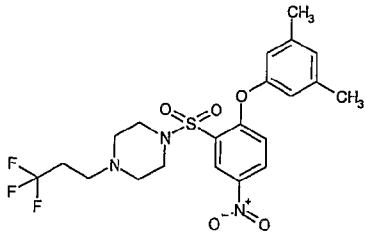
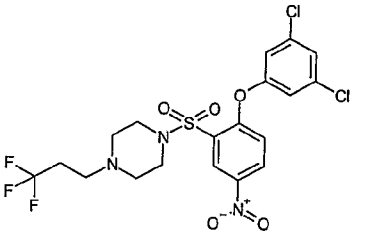
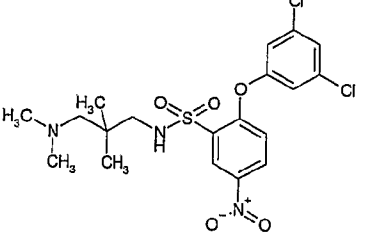
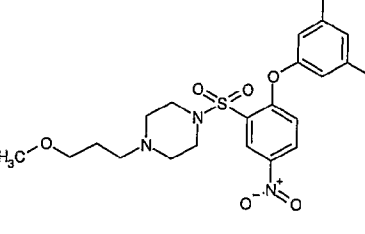
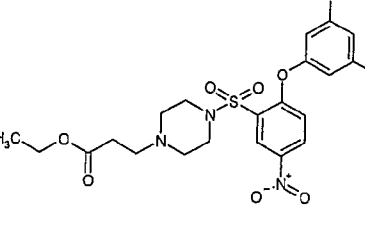
- 104 -

4-23		460.33923	460		A	A
4-24	 ClH	469.99141	434	262-264	A	A
4-25		482.34559	483	226	B	
4-26		475.56808	476	178-179	A	A
4-27		516.40396	517	182-183	A	A

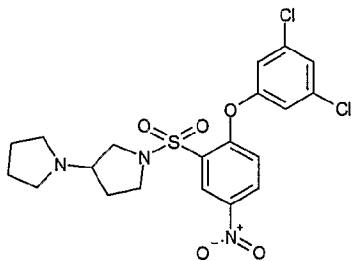
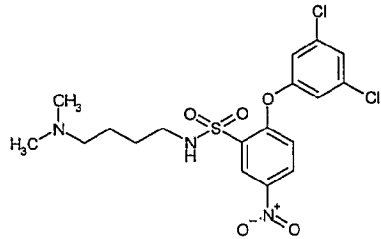
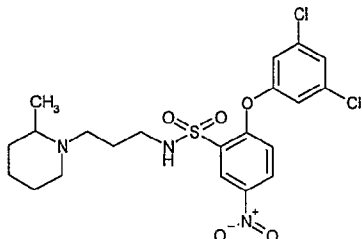
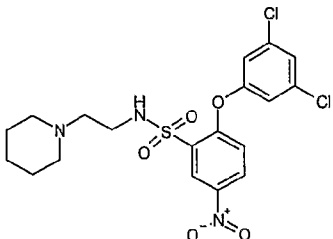
- 105 -

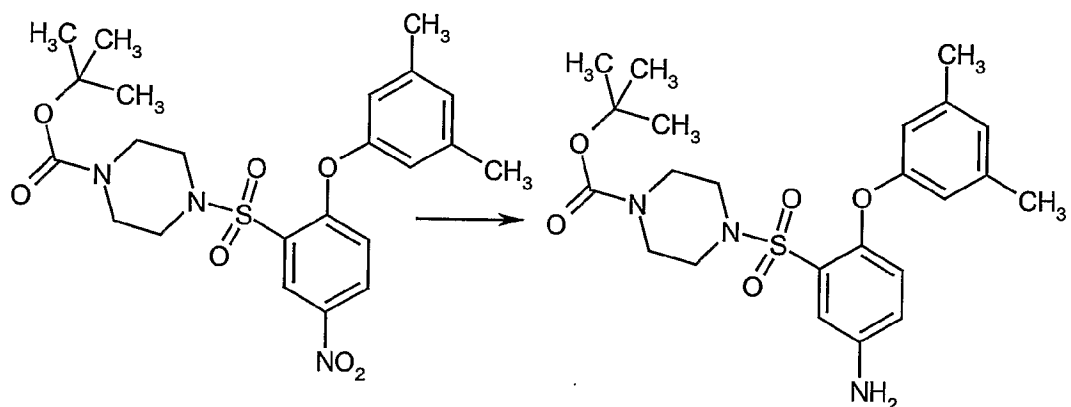
4-28		491.63268	492	143-144		A
4-29		514.43165	515	173-174	A	A
4-30		531.46226	531	98-99		A
4-31		503.40808	503	138-140		A
4-32		529.44632	529	167-169		A

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4-33		487.50173	488		A	A
4-34		528.33761	528	166-167	A	A
4-35		476.38226	476	134		A
4-36		504.39281	504	145	A	A
4-37		532.40336	532	160-162		A

- 107 -

4-38		486.37747	486		A	A
4-39		462.35517	462			A
4-40		502.4205	502			A
4-41		474.36632	474			A

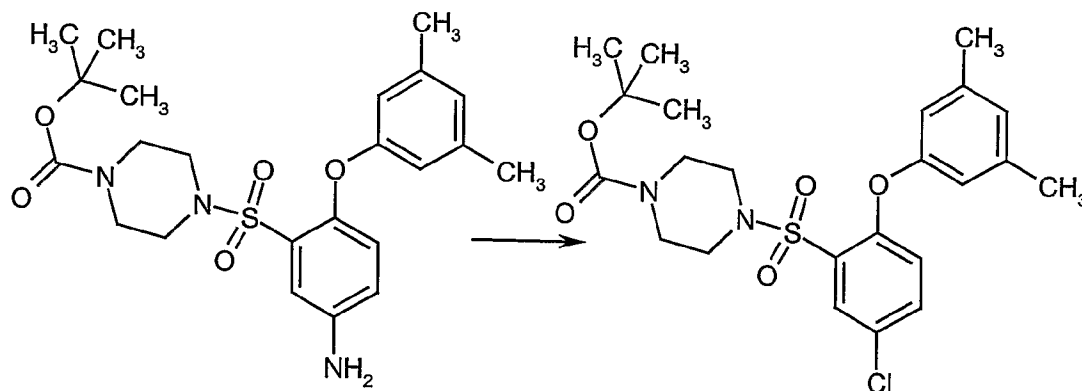
Example 5-1

- 5 (1) The mixture of tert-butyl 4-[[2-(3,5-dimethylphenoxy)-5-nitrophenyl]-sulfonyl]-1-piperazinecarboxylate (6.80g, 13.83 mmol), which was prepared in the step (2) of Example 1-1 and 10% Pd-C (1) in methanol (600 ml) was stirred at room temperature under 1 ATM of H₂ for 5 hrs. The Pa-C was filtered off. The filtrate was evaporated to 30 ml. The produced crystals was
- 10 collected by filtration to give tert-butyl 4-[[5-amino-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (6.0 g, 94.0%).: HPLC-MS (ESI): Calcd for C₂₃H₃₁N₃O₅S [M + H]⁺ 462, Found: 462.

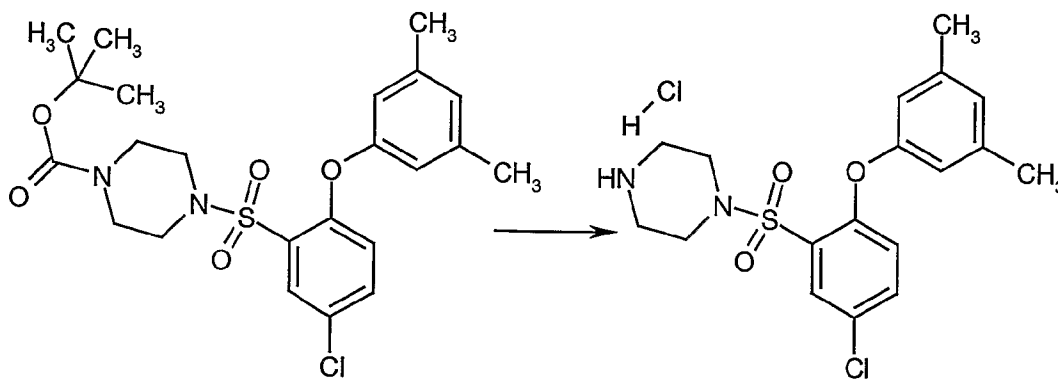
Molecular weight: 461.5846

15 Activity grade RBA: C

Activity grade Ca²⁺: C

Example 5-2

- 5 (1) To the mixture of copper(I) chloride (39.6 mg, 0.4 mmol) and *tert*-butyl nitrite (41.2 mg, 0.4 mmol) in CH₃CN (10 ml) was added *tert*-butyl 4-{[5-amino-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (92.3 mg, 0.2 mmol) which was prepared in the Example 5-1 at 60°C. The mixture was stirred at 65-70°C for 2hrs, and cooled to room temperature. The solvent was evaporated. CH₂Cl₂ was added to the residue and the mixture was washed with 15 ml of 4N NaOH, 30 ml of brine, successively, dried over MgSO₄. The solvent was evaporated, and the residue was purified by preparative TLC on silica gel (CH₂Cl₂/CH₃OH =35/1) to give *tert*-butyl-4-
10 {[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (56.0 mg, 58.2%) .
15



- 110 -

- (2) To the suspension of *tert*-butyl 4-{{[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (40.0 mg, 0.08 mmol) in dry CH₂Cl₂ (1.5 ml) was added 0.3 ml of 4N hydrogen chloride solution in 1,4-dioxane, the mixture was stirred for 5 hrs at room temperature. The solvent was evaporated, and diethyl ether (5 ml) was added to the residue. The produced precipitate was collected by filtration and dried to give 1-{{[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}piperazine hydrochloride (24.0 mg, 69.2%): mp 202-204 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.30 (6H, s), 3.14 (4H, be), 3.50 (4H, br), 6.82 (2H, s), 6.91 (1H, s), 6.97 (1H, d, J = 8.7 Hz), 7.70 (1H, t, J = 8.7 Hz), 7.82 (1H, d, J = 2.3 Hz), 9.57 (2H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₁ClN₂O₃S [M + H]⁺ 381, Found: 381.

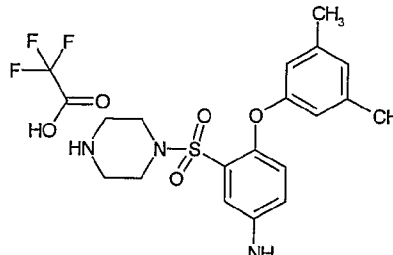
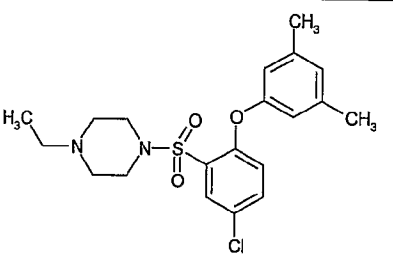
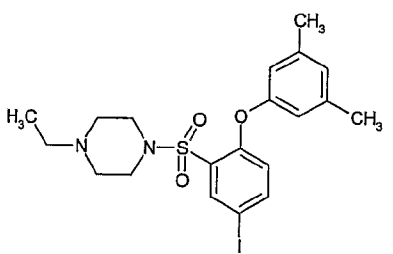
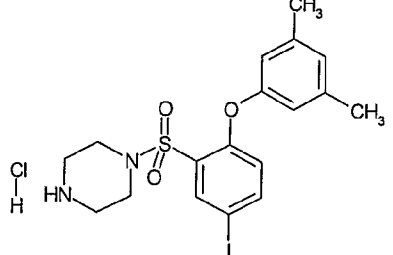
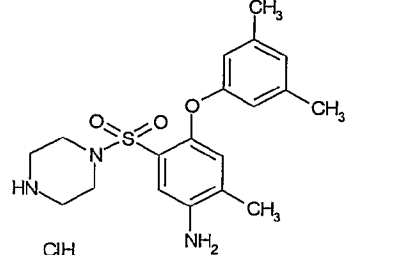
Molecular weight: 417.3576

Activity grade RBA: A

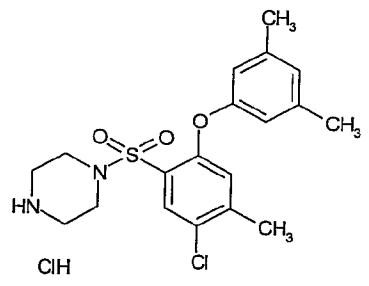
15 Activity grade Ca²⁺: A

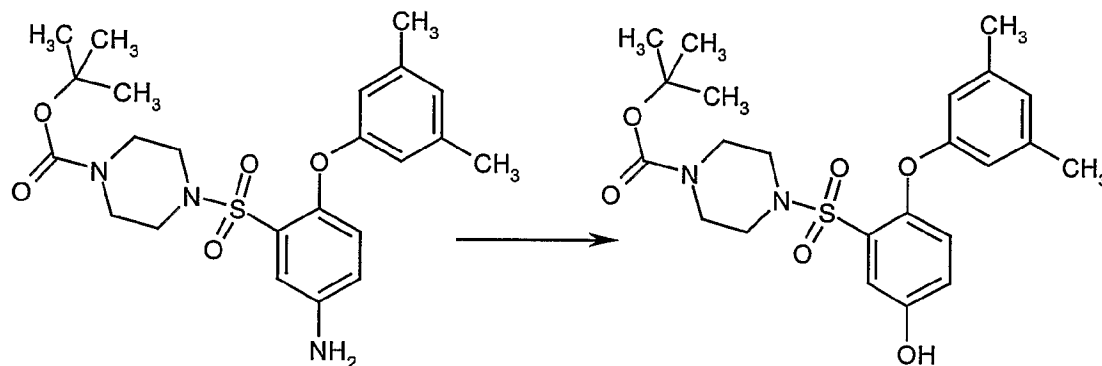
In the similar manner as described in Example 5-1 or 5-2 above, compounds in Example 5-3 to 5-8 as shown in Table 5 were synthesized.

Table 5

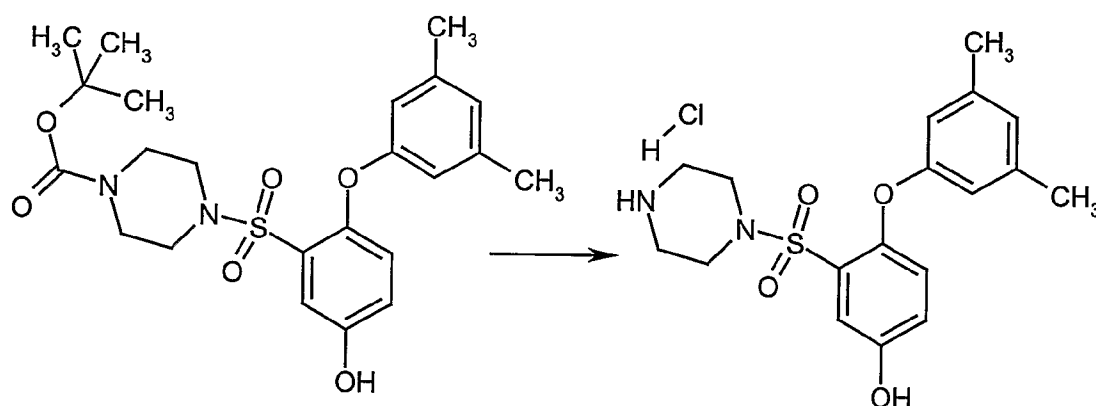
EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
5-3		475.49058	362	133-135	C	C
5-4		408.95085	409	120-122	A	A
5-5		500.40225	501	133-134	A	A
5-6		508.80904	473	241-243	A	A
5-7		448.41534	376	183	C	C

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5-8	 ClH	431.38473	395	148		A
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Example 6-1

- 5 (1) To the solution of *tert*-butyl 4-[[5-amino-2-(3,5-dimethylphenoxy)phenyl]-sulfonyl]-1-piperazinecarboxylate (138.5mg, 0.30 mmol) prepared in the step (1) of Example 5-1 in CH₂Cl₂ (5 ml) was added nitrosonium tetrafluoroborate (38.5 mg, 0.33 mmol) at 0 °C and the solution was stirred at 0°C for 30 min. The solvent was evaporated. The residue was dissolved in methanol (5 ml)
- 10 and the solution of Cu₂O (64.4 mg, 0.45 mmol) and CuSO₄·3H₂O (724.8 mg, 3 mmol) in 10ml of water was added to the above solution at 0°C. The mixture was stirred at 0°C for 30 min. The solvent was evaporated and ethyl acetate was added. The mixture was washed with 1 N aqueous NaOH, brine, successively and dried over MgSO₄. The solvent was evaporated and the residue was purified by preparative TLC on silica gel (CH₂Cl₂/CH₃OH =
- 15 20/1) to give *tert*-butyl 4-[[2-(3,5-dimethylphenoxy)-5-hydroxyphenyl]sulfonyl]-1-piperazinecarboxylate (39.0 mg , 28.1%).

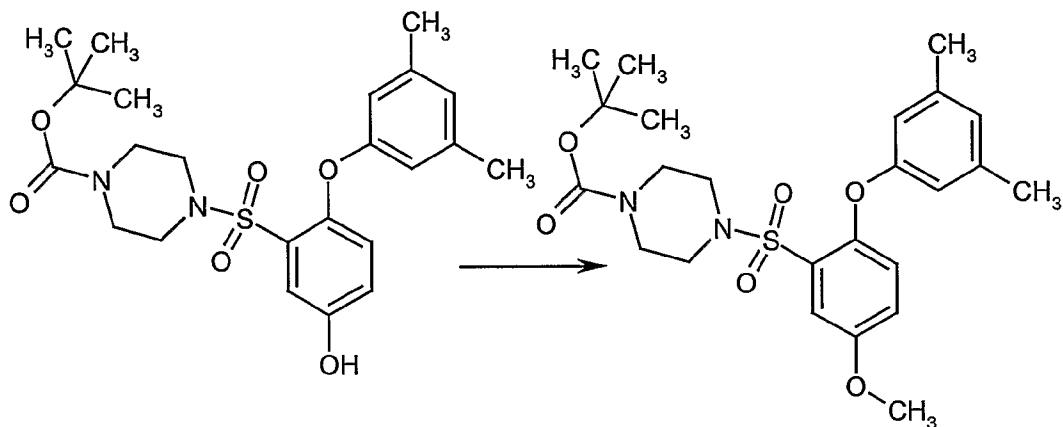


- (2) To the suspension of *tert*-butyl 4-[[2-(3,5-dimethylphenoxy)-5-hydroxyphenyl]sulfonyl]-1-piperazinecarboxylate (12.0 mg, 0.03 mmol) in dry CH_2Cl_2 (1ml) was added 4 N HCl solution in 1,4-dioxane (0.18 ml), the mixture was stirred 5hrs at room temperature. The solvent was evaporated, and 3ml of diethyl ether was added to the residue. The precipitate was collected by filtration and dried to give 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)phenol hydrochloride (9.0 mg, 87.0%): mp >286; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.24 (6H, s), 3.12 (4H, br), 3.36 (4H, br), 6.56 (2H, s), 6.76 (1H, s), 6.96 (1H, d, $J = 9$ Hz), 7.08 (1H, q, $J = 9$ Hz), 7.25 (1H, d, $J = 2.6$ Hz), 9.03 (2H, br), 10.06 (1H, s); HPLC-MS (ESI): Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 363, Found: 363.

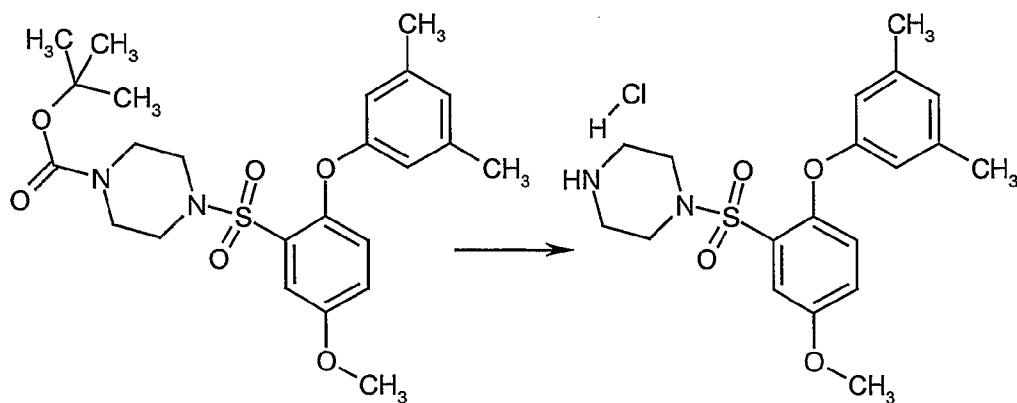
15 Molecular weight: 398.9120

Activity grade RBA: C

Activity grade Ca^{2+} : C

Example 6-2

- 5 (1) To the solution of *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-5-hydroxyphenyl]sulfonyl}-1-piperazinecarboxylate (20.0 mg, 0.04 mmol), which was prepared in the step (1) of Example 6-1 in dry DMF (1ml) was added methyl iodide (30.7 mg, 0.22 mmol) and K₂CO₃ (12.0 mg, 0.09 mmol). The mixture was stirred at room temperature for 3 hrs. The solvent was evaporated *in vacuo* and 3ml of ice water was added. The white precipitate was collected by
 10 filtration and washed with 1 N aqueous NaOH, water and dried to give *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-5-methoxyphenyl]sulfonyl}-1-piperazinecarboxylate as white powder (20.0 mg, 97.1%).



- (2) To the solution of *tert*-butyl 4-[[2-(3,5-dimethylphenoxy)-5-methoxyphenyl]-sulfonyl]-1-piperazinecarboxylate (18.0 mg, 0.04 mmol) in dry CH₂Cl₂ (1 ml) was added 4 N HCl (0.2 ml) solution in 1,4-dioxane, the mixture was stirred 5 hrs at room temperature. The solvent was evaporated, and 3 ml of diethyl ether was added to the residue. The precipitate was collected by filtration and dried to give 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)phenol hydrochloride (12.0 mg, 76.9%): mp 175-177°C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.25 (6H, s), 3.12 (4H, t, J = 4.5 Hz), 3.40 (4H, d, J = 4.5 Hz), 3.82 (3H, s), 6.62 (2H, s), 6.80 (1H, s), 7.04 (1H, d, J = 9.1 Hz), 7.27 (1H, q, J = 9.1 Hz), 7.33 (1H, d, J = 3.0 Hz), 9.24 (2H, br);

HPLC-MS (ESI): Calcd for C₁₉H₂₄N₂O₄S [M + H]⁺ 377, Found: 377.

Molecular weight: 412.9391

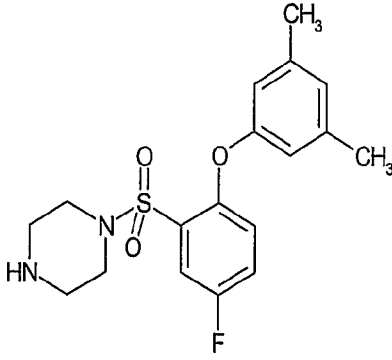
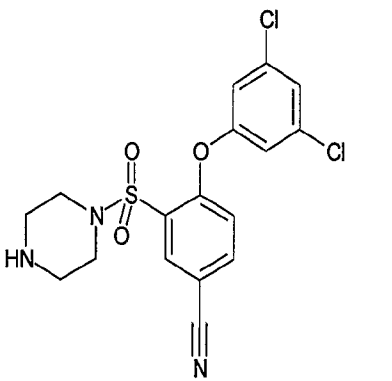
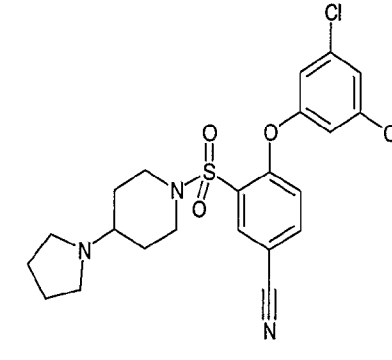
Activity grade RBA: A

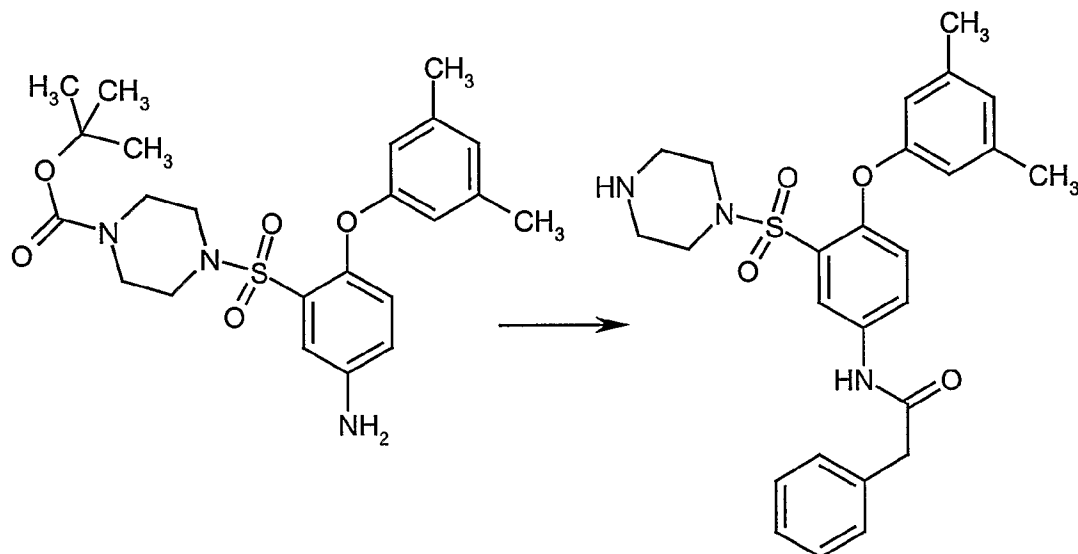
15 Activity grade Ca²⁺: B

In the similar manner as described in Example 6-1 or 6-2 above, compounds in Example 6-3, 6-4 and 6-5 as shown in Table 6 were synthesized.

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Table 6

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
6-3		364.4421	365	116-118	A	A
6-4		412.2974	412	179-181	9	7
6-5		480.4169	480	186-187	20	17

Example 7-1

- 5 (1) To the mixture of *tert*-butyl 4-[[5-amino-2-(3,5-dimethylphenoxy)phenyl]-sulfonyl]-1-piperazinecarboxylate (369 mg, 0.80 mmol), which was prepared in the step (1) of Example 5-1, and triethylamine (97 mg, 0.96 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise the solution of phenylacetyl chloride (130 mg, 0.84 mmol) in THF (5 ml) at 0°C with stirring. The mixture was then stirred at RT for 3 hrs, and CH_2Cl_2 was added. The mixture was washed with 0.5 N aqueous HCl, brine, saturated aqueous NaHCO_3 , brine, successively, dried over MgSO_4 . The solvent was evaporated. Dry CH_2Cl_2 (15 ml) was added to the residue. 4 N HCl solution in 2,4-dioxane (1ml) was added to the solution at 0°C with stirring. The mixture was then stirred at room temperature for 3 hrs. The obtained precipitate was collected to give product as HCl salt. The HCl salt was suspended in 10 ml of ice water and the PH of the mixture was adjusted to 8 by addition of saturated aqueous NaHCO_3 , extracted by CH_2Cl_2 . The combined extract was washed with saturated aqueous NaHCO_3 , brine, successively, dried over MgSO_4 . The solvent was evaporated. 5 ml of methanol was added to the residue and the white precipitate was collected by filtration and washed with ether and dried to give
- 10
- 15
- 20

5 N-[4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)phenyl]-2-phenylacet-
amide (330 mg, 86.0%): mp 228-230°C; ¹H NMR (300 MHz, CDCl₃). 2.28
(6H, s), 2.87 (4H, br), 3.24 (4H, br), 3.74 (2H, s), 6.62 (2H, s), 6.79 (1H, s),
6.87 (1H, d, J = 8.8 Hz), 7.34-7.62 (6H, m), 7.62 (1H, s), 7.95 (1H, q, J = 8.8
Hz); HPLC-MS (ESI): Calcd for C₂₆H₂₉N₃O₄S [M + H]⁺ 480, Found: 480.

Molecular weight: 479.6027

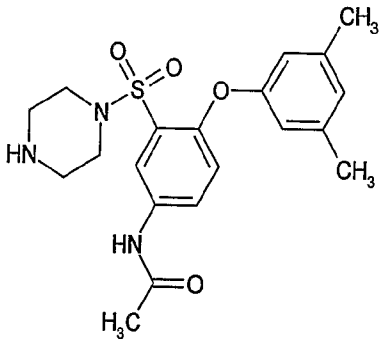
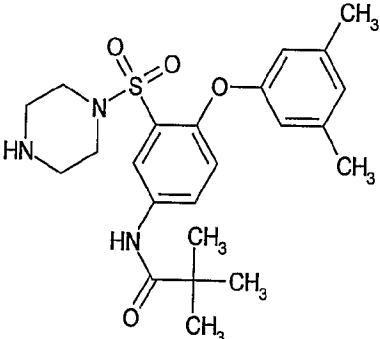
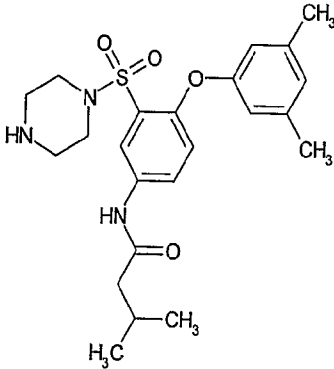
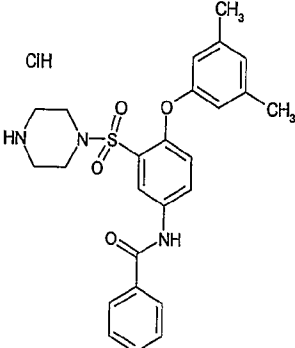
Activity grade RBA: C

Activity grade Ca²⁺: C

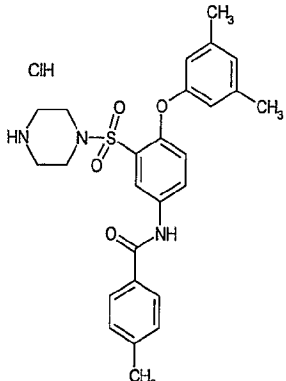
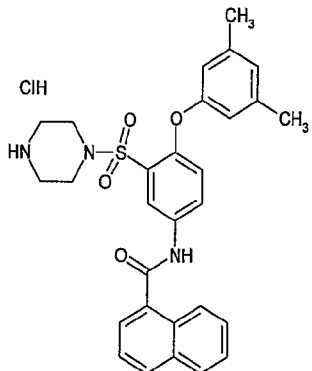
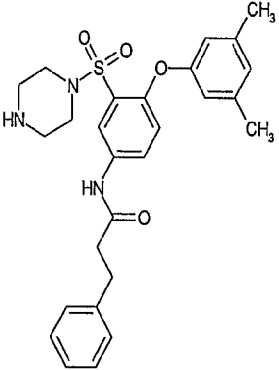
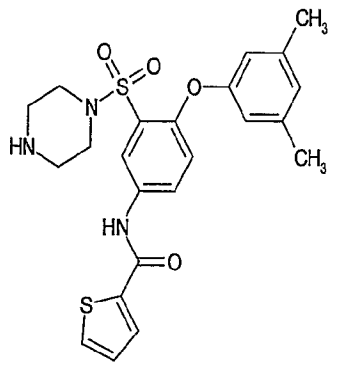
10

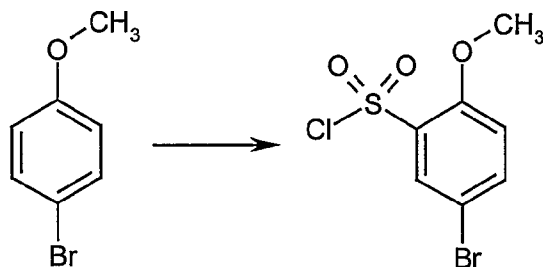
In the similar manner as described in Example 7-1 above, compounds in Example 7-
2 to 7-9 as shown in Table 7 were synthesized.

Table 7

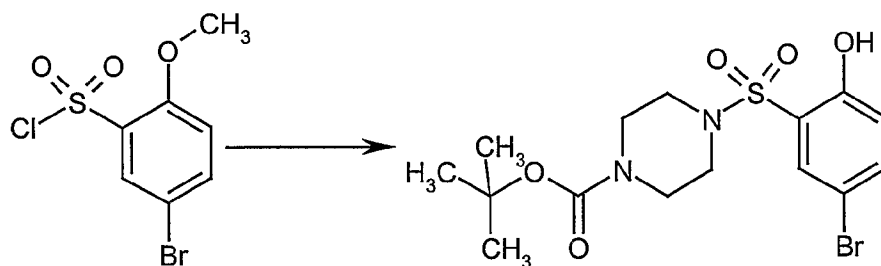
EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
7-2		403.504	404		C	C
7-3		445.5852	446		C	C
7-4		445.5852	446		C	C
7-5		502.0366	466		C	C

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7-6		516.0637	484		C	C
7-7		552.0972	516		C	B
7-8		493.6298	494		C	C
7-9		471.6014	472		C	C

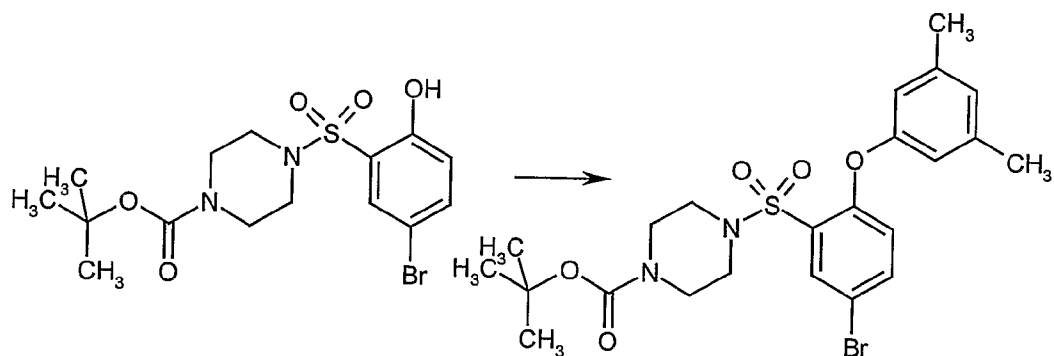
Example 8-1

- 5 (1) To a solution of 4-bromoanisole (2.00 g, 10.7 mmol) in CHCl_3 (20 ml) was added chlorosulfonic acid (1.49 ml, 22.5 mmol) at 0°C . This mixture was stirred at room temperature for 2 hrs, and then poured into ice water (50 ml). This mixture was extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated to give crude 5-bromo-2-methoxybenzenesulfonyl chloride (0.760 g, 24.9%).
- 10



- 15 (2) To a solution of 5-bromo-2-methoxybenzenesulfonyl chloride (760 mg, 2.66 mmol) and Et_3N (445 μl , 3.19 mmol) in CH_2Cl_2 (20 ml) was added 1-(*t*-butoxycarbonyl)piperazine (521 mg, 2.80 mmol) at 0°C . This mixture was stirred at room temperature for 6 hrs, and then diluted with Et_2O , washed with 10% citric acid solution, aqueous NaHCO_3 , and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated to give crude sulfonamide (716 mg).
- 20

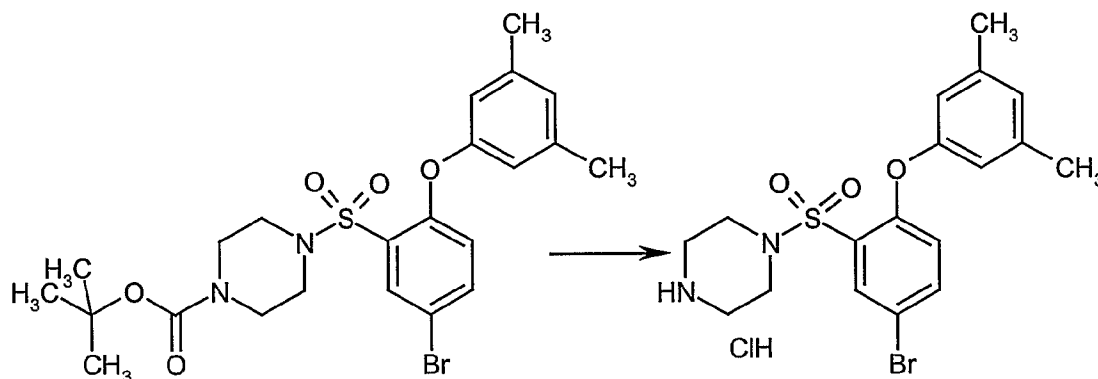
To a solution of the sulfonamide (716 mg, 1.65 mmol) in CH_2Cl_2 (5 ml) was added 1M BBr_3 solution in CH_2Cl_2 (3.30 ml, 3.30 mmol) at 0°C . This mixture was stirred at 0°C for 1 hr. After basifying with 3M aqueous NaOH (20 ml), THF (15 ml) and Di-*t*-butyl dicarbonate (718 mg, 3.29 mmol) were added to the mixture at 0°C . The mixture was stirred at room temperature overnight. This mixture was extracted with Et_2O . The organic extract was dried over anhydrous Na_2SO_4 , filtered, and concentrated to give di(Boc)-compound. To hydrolyze *t*-butyl carbonate, the residue was treated with K_2CO_3 (455 mg, 3.29 mmol) in MeOH (10 ml) at room temperature for 5 hrs. After removing MeOH by evaporation, the residue was acidified with 10% citric acid solution. This aqueous mixture was extracted with EtoAc. The organic extract was dried over anhydrous Na_2SO_4 , filtered, and concentrated to give *tert*-butyl 4-[(5-bromo-2-hydroxyphenyl)sulfonyl]-1-piperazinecarboxylate (526 mg, 47.0%).



- (3) To a mixture of *tert*-butyl 4-[(5-bromo-2-hydroxyphenyl)sulfonyl]-1-piperazinecarboxylate (410 mg, 0.973 mmol), 3,5-dimethylphenylbromic acid (219 mg, 1.46 mmol), $\text{Cu}(\text{OAc})_2$ (177 mg, 0.973 mmol), and powdered 4A molecular sieves (820 mg) in CH_2Cl_2 (10 ml) was added Et_3N (0.678 ml, 4.87 mmol) at room temperature. This mixture was stirred at room temperature under ambient atmosphere overnight. The resulting slurry was filtered through Celite. The filtrate was diluted with EtoAc, and washed with aqueous NH_4Cl , NaHCO_3 , and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated. Et_2O was added to the residue.

The resulting precipitate was collected by filtration, and washed with Et₂O. This solid was purified by column chromatography on silica gel (CHCl₃/MeOH=99/1) to give *tert*-butyl 4-[[5-bromo-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (320 mg, 62.6%).

5

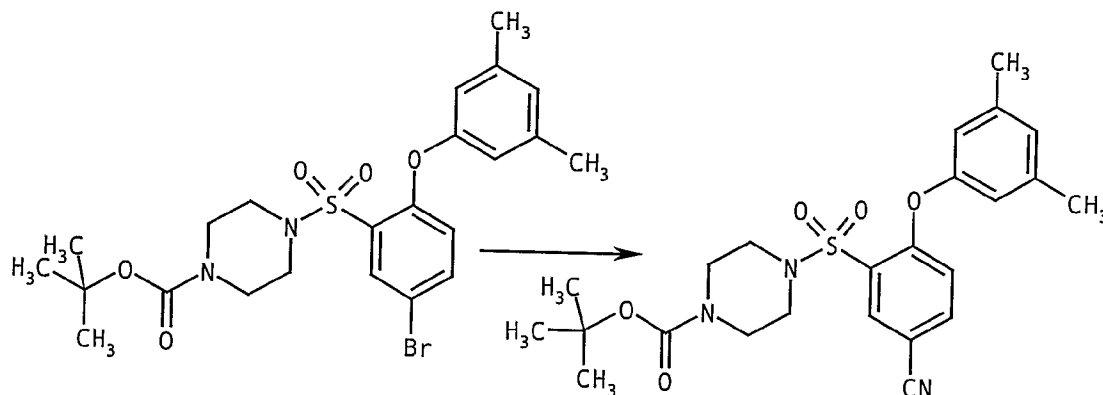


- (4) To a solution of *tert*-butyl 4-[[5-bromo-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (25.0 mg, 48.0 μ mol) in CH₂Cl₂ (1.0 ml) was added 4M HCl solution in 1,4-dioxane (100 μ l, 400 μ mol) at 0°C. This mixture was stirred at room temperature overnight. Solvents were removed by evaporation. The resulting residue was suspended in Et₂O, and collected by filtration to give a white amorphous, 1-[[5-bromo-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]piperazine hydrochloride (20.0 mg, 90.2%): ¹H NMR (300 MHz, CDCl₃) δ 2.31 (6 H, s), 3.12-3.38 (4H, br), 3.60-3.84 (4H, br), 6.72 (2H, s), 6.75 (1H, d, *J* = 8.7 Hz), 6.87 (1H, s), 7.54 (1H, dd, *J* = 2.3, 8.7 Hz), 8.05 (1H, d, *J* = 2.3 Hz), 9.79-10.40 (2H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₁BrN₂O₃S [M + H]⁺ 425 and 427, Found: 425 and 427.

20 Molecular weight: 461.8086

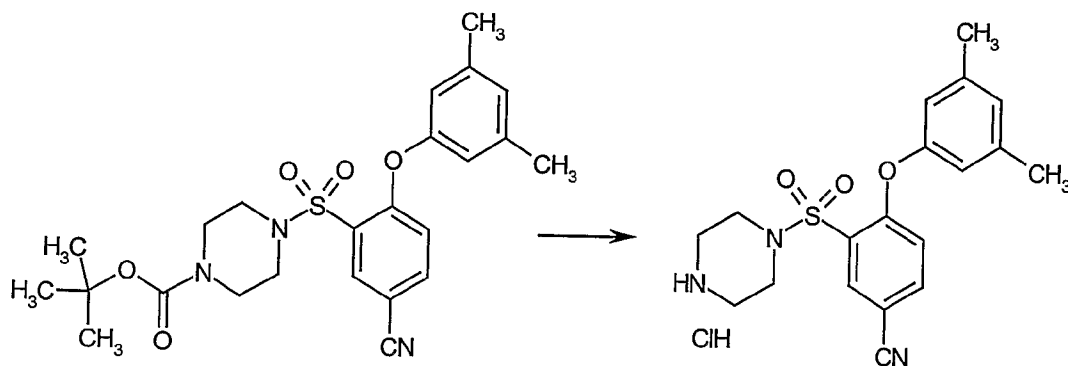
Activity grade RBA: A

Activity grade Ca²⁺: A

Example 9-1

- 5 (1) A mixture of *tert*-butyl 4-{[5-bromo-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (95.0 mg, 181 μ mol), which was prepared in the step (3) of Example 8-1, CuCN (32.4 mg, 362 μ mol), and Pd(PPh₃)₄ (20.9 mg, 18.1 μ mol) in DMF (2 ml) was heated at 150°C overnight. After cooling to room temperature, this mixture was diluted with CH₂Cl₂, and washed with ammonia solution and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtoAc=3/1~2/1) to give *tert*-butyl 4-{[5-cyano-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (14.0 mg, 16.4%).

15



- (2) To a solution of *tert*-butyl 4-{[5-cyano-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (14.0 mg, 29.7 μ mol) in CH₂Cl₂ (1.0 ml)

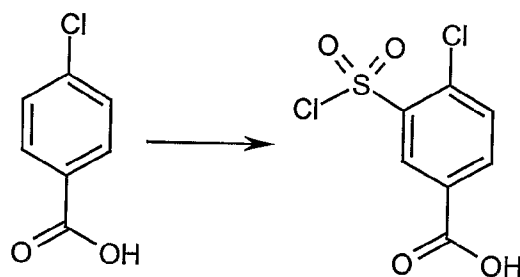
was added 4M HCl solution in dioxane (0.2 ml) at room temperature. This mixture was stirred at room temperature overnight. Dioxane was removed by evaporation. The residue was suspended in Et₂O. The resulting precipitate was collected by filtration to give 4-(3,5-dimethylphenoxy)-3-(1-piperazinyl-sulfonyl)benzonitrile hydrochloride (6.0 mg, 49.6 %): ¹H NMR (300 MHz, CDCl₃) δ 2.34 (6 H, s), 3.28-3.47 (4H, br), 3.67-3.83 (4H, br), 6.78 (2H, s), 6.89 (1H, d, *J* = 8.6 Hz), 6.95 (1H, s), 7.69 (1H, dd, *J* = 1.9, 8.6 Hz), 8.24 (1H, d, *J* = 1.9 Hz), 9.97-10.32 (2H, br); HPLC-MS (ESI): Calcd for C₁₉H₂₁N₃O₃S [M + H]⁺ 372, Found: 372.

Molecular weight: 407.9225

Activity grade RBA: A

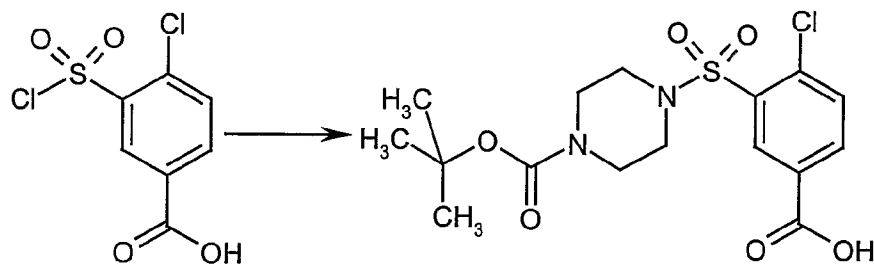
Activity grade Ca²⁺: A

Example 10-1

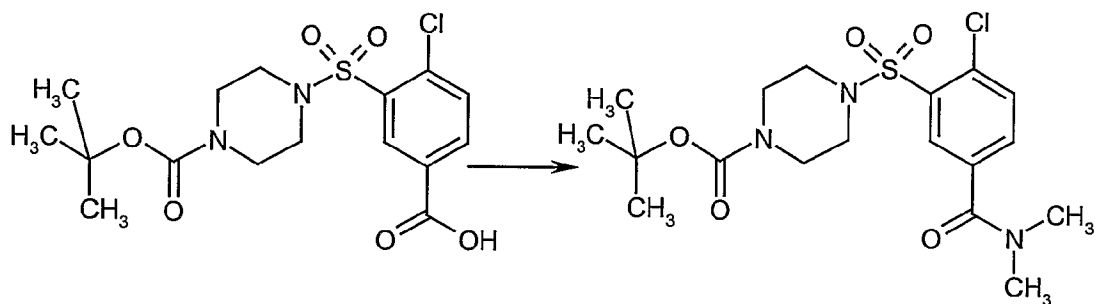


- (1) To 4-chlorobenzoic acid (1.00 g, 6.39 mmol) was added chlorosulfonic acid (2.55 ml, 38.3 mmol) at room temperature dropwise. This mixture was heated at 150°C for 6 hrs. After cooling to room temperature, the mixture was diluted with CH₂Cl₂. This solution was added to ice water. Two phases were separated. The organic phase was washed with brine, and then dried over anhydrous MgSO₄, filtered, and concentrated to give crude 4-chloro-3-(chlorosulfonyl)benzoic acid (0.720 g, 43.9%).

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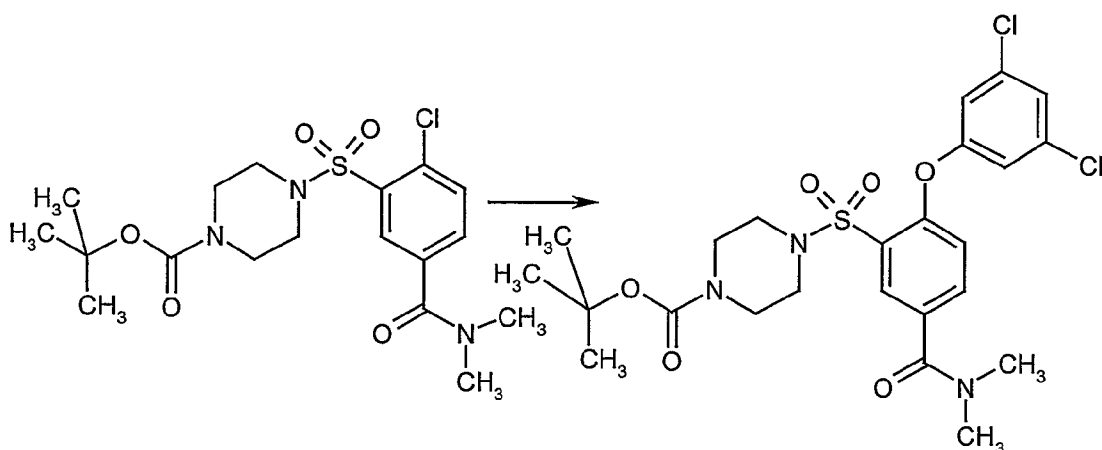
- (2) To a solution of 4-chloro-3-(chlorosulfonyl)benzoic acid (200 mg, 0.784 mmol) and Et₃N (130 μ l, 0.938 mmol) in CH₂Cl₂ (5 ml) was added 1-(*t*-butoxycarbonyl)piperazine (161 mg, 0.864 mmol) at 0°C. This mixture was stirred at room temperature overnight, and then diluted with CH₂Cl₂, washed with 10% citric acid solution. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was suspended in Et₂O, and the precipitate was collected by filtration to give crude 3-{[4-(*tert*-butoxycarbonyl)-1-piperazinyl]sulfonyl}-4-chlorobenzoic acid (200 mg, 63.0%).



- (3) To a mixture of 3-{[4-(*tert*-butoxycarbonyl)-1-piperazinyl]sulfonyl}-4-chlorobenzoic acid (340 mg, 0.840 mmol), dimethylammonium chloride (137 mg, 1.68 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (193 mg, 1.01 mmol), and HOBT (136 mg, 1.01 mmol) in CH₂Cl₂ was added Et₃N (410 μ l, 2.96 mmol) at 0°C. This mixture was stirred at room temperature for two days. The mixture was diluted with EtOAc, and washed with 10% citric acid solution, aqueous NaHCO₃, and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated.

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The residue was purified by column chromatography on silica gel (EtoAc) to give *tert*-butyl 4-({2-chloro-5-[(dimethylamino)carbonyl]phenyl}sulfonyl)-1-piperazinecarboxylate (258 mg, 71.1%).

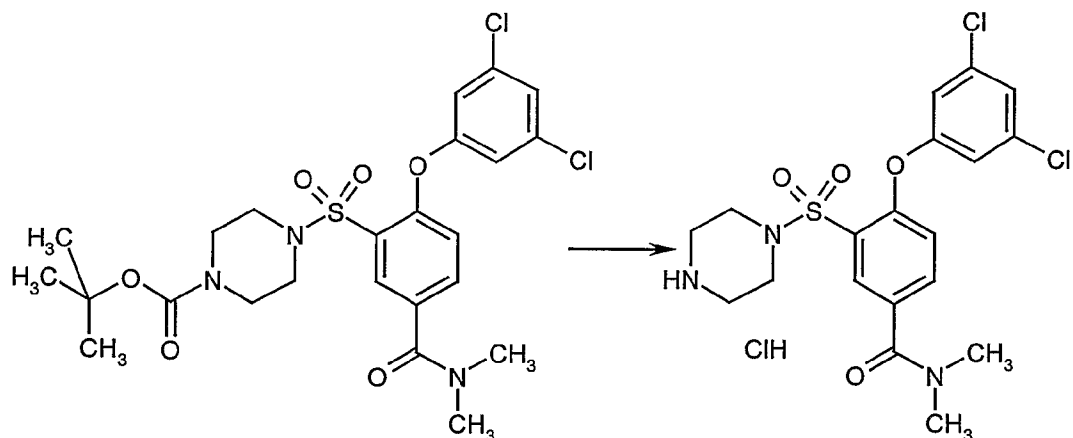


5

- (4) To a mixture of *tert*-butyl 4-({2-chloro-5-[(dimethylamino)carbonyl]phenyl}sulfonyl)-1-piperazinecarboxylate (248 mg, 0.574 mmol) and 3,5-dimethylphenol (140 mg, 0.859 mmol) in DMF (2 ml) was added *t*-BuOK (129 mg, 1.15 mmol) at room temperature. This mixture was heated at 150°C for two days. After cooling to room temperature, ice water (10 ml) was added to the mixture. Two phases were separated. The aqueous phase was extracted with CH₂Cl₂. The combined organic layers were washed with aqueous NaHCO₃ and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. This residue was purified by column chromatography on silica gel (Hexane/-EtoAc=1/2) to give *tert*-butyl 4-({2-(3,5-dichlorophenoxy)-5-[(dimethylamino)carbonyl]phenyl}sulfonyl)-1-piperazinecarboxylate (182 mg, 56.8%).

10

15



- (5) To a solution of *tert*-butyl 4-({2-(3,5-dichlorophenoxy)-5-[(dimethylamino)-carbonyl]phenyl}sulfonyl)-1-piperazinecarboxylate (150 mg, 0.269 mmol) in CH_2Cl_2 was added 4M HCl solution in dioxane (0.300 ml, 1.20 mmol) at 0°C . This mixture was stirred at room temperature overnight. Solvents were removed by evaporation. The resulting residue was suspended in Et_2O and collected by filtration to give 4-(3,5-dichlorophenoxy)-N,N-dimethyl-3-(1-piperazinylsulfonyl)benzamide hydrochloride (50.0 mg, 37.6%): mp $197\text{--}199^\circ\text{C}$; HPLC-MS (ESI): Calcd for $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 458, Found: 458.

Molecular weight: 494.8279

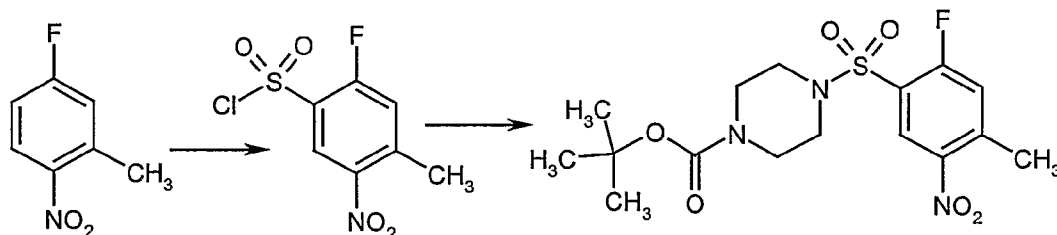
Activity grade RBA: B

15 Activity grade Ca^{2+} : B

In the similar manner as described in Example 10-1 above, compound in Example 10-2 as shown in Table 10 was synthesized.

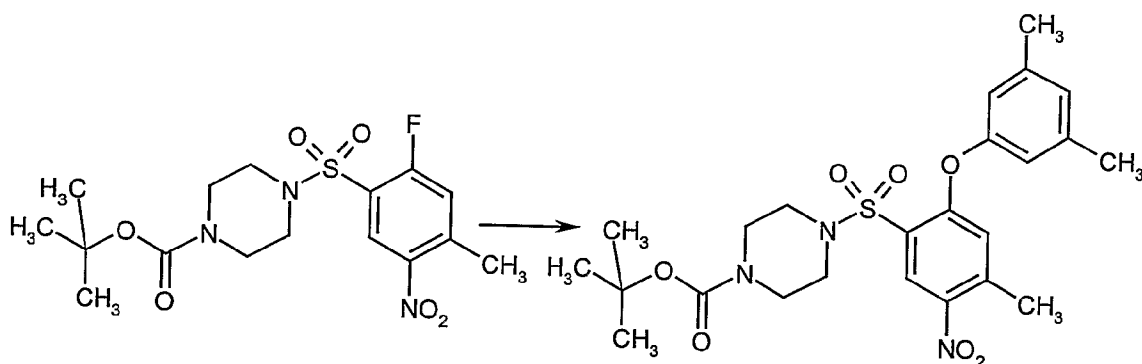
Table 10

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
10-2	 ClH	490.0443	454	242-247	B	A

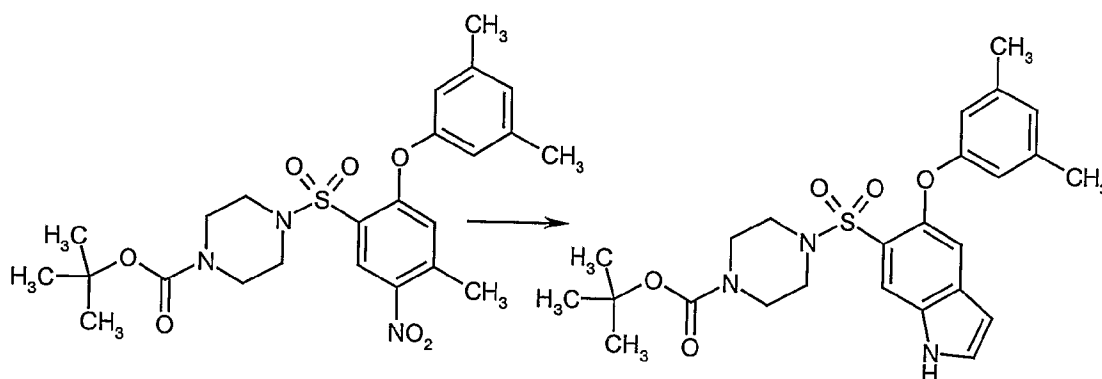
Example 11-1

- 5 (1) To a mixture of 5-fluoro-2-nitrotoluene (1.00 g, 6.45 mmol) in CHCl₃ (10 ml) was added chlorosulfonic acid (0.86 ml, 12.9 mmol) dropwise. The mixture was refluxed overnight. After the mixture was cooled to room temperature, the mixture was diluted with CHCl₃, then ice water was added to the mixture. The organic layer was extracted with CHCl₃ and was washed with brine. The extracted organic layer was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give a pale yellow oil.

The oil was dissolved in THF (50 ml). To the solution was added *tert*-butyl 1-piperazinecarboxylate (1.20 g, 6.45 mmol), and N,N-diisopropylethylamine (1.12 ml, 6.45 mmol) successively. The mixture was stirred at room temperature for 4 hrs. The mixture was concentrated *in vacuo*. The residue was diluted with ethylacetate and was washed with brine. The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtoAc/Hexane) to give *tert*-butyl 4-[(2-fluoro-4-methyl-5-nitrophenyl)sulfonyl]-1-piperazine-carboxylate (1.00 g, 38.4 %) as a pale brown solid.

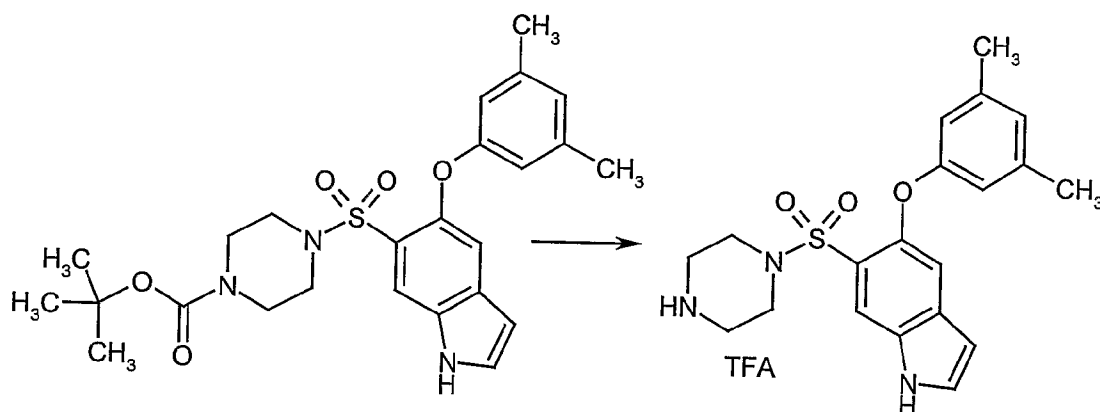


- (2) To a solution of 3,5-dimethylphenol (33.3mg, 0.27 mmol) in 1,4-dioxane (1 ml) was added sodium hydride (60 % oil suspension, 11.9 mg, 0.30 mmol) portionwise. The mixture was stirred at room temperature for 30 minutes. To the mixture was added a solution of *tert*-butyl 4-[(2-fluoro-4-methyl-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (100 mg, 0.25 mmol) in 1,4-dioxane (1 ml) slowly. The mixture was stirred at 70°C overnight. After the mixture was cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was washed with ice water, then was dried *in vacuo* to give *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-4-methyl-5-nitrophenyl]sulfonyl}-1-piperazinecarboxylate (92.8 mg, 74.1 %) as a white solid.



- (3) *tert*-butyl 4-{[2-(3,5-dimethylphenoxy)-4-methyl-5-nitrophenyl]sulfonyl}-1-piperazinecarboxylate (186 mg, 0.368 mmol) was placed in a frame-dried two-necked flask. It was dried *in vacuo*, then was purged with argon. To the flask was added dry DMF, dimethylformamide dimethyl acetal (0.0585 ml,

0.441 mmol), and pyrrolidine 0.0369 ml, 0.441 mmol). The mixture was stirred at 110°C for 3 hrs. Additional pyrrolidine (0.0185 ml, 0.22 mmol) was added to the mixture. The mixture was stirred at 110°C for additional 1 hr. After the mixture was cooled to room temperature, the mixture was transferred to a solution of 4 M aqueous ammonium acetate in DMF, using additional DMF to rinse the mixture into the reaction flask. To the solution was added 20 % w/v aqueous titanium (III) chloride (1.50 ml, 1.98 mmol) dropwise. The suspension was stirred at room temperature for 15 minutes. The mixture was made basic with 1N aqueous NaOH solution. The mixture was diluted with diethylether. The mixture was filtered, then the organic layer was extracted with diethylether, was washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtoAc/Hexane) to give *tert*-butyl 4-{[5-(3,5-dimethylphenoxy)-1H-indol-6-yl]sulfonyl}-1-piperazinecarboxylate (42.2 mg, 23.6 %) as a pale brown solid.



(4) To a solution of *tert*-butyl 4-{[5-(3,5-dimethylphenoxy)-1H-indol-6-yl]sulfonyl}-1-piperazinecarboxylate (15.4 mg, 0.0317 mmol) in CH₂Cl₂ (1 ml) was added trifluoroacetic acid (0.10 ml) at 0°C. The mixture was stirred at 0°C for 2 hrs. Toluene was added to the mixture, then was concentrated *in vacuo*. The residue was triturated with diethylether to give 5-(3,5-dimethyl-

phenoxy)-6-(1-piperazinylsulfonyl)-1H-indole trifluoroacetate (12.7 mg, 80.2%).

HPLC-MS (ESI): Calcd for $C_{20}H_{23}N_3O_3S$ $[M+H]^+$ 368, Found: 368.

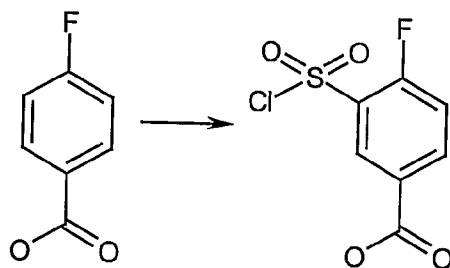
5 Molecular weight: 499.5129

Activity grade RBA: C

Activity grade Ca^{2+} : C

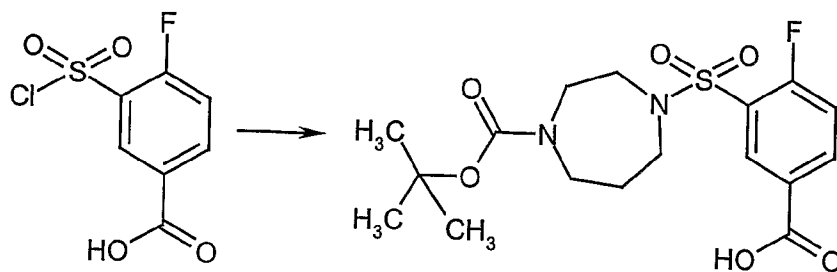
Example 12-1

10

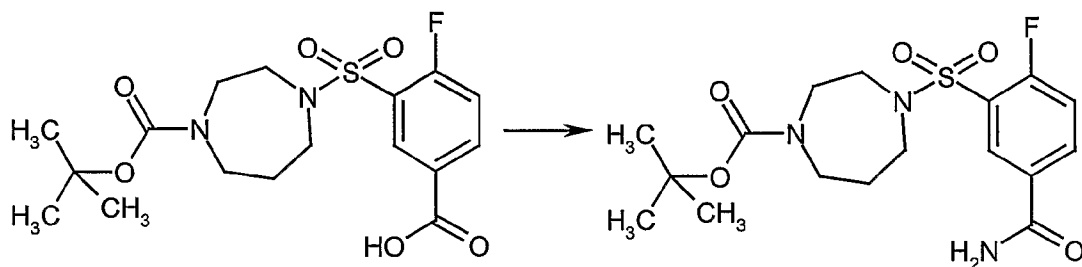


- 15 (1) 4-Fluorobenzoic acid (5.0 g, 35.7 mmol) was added to chlorosulfonic acid (31.5 g, 0.27 mol), and the mixture was stirred at 150°C for 2hrs. After cooling to room temperature, the mixture was poured into ice-water dropwise with cooling. The resulting white precipitate was collected by filtration. The solid was washed with water, and dried in vacuo to give 3-(chlorosulfonyl)-4-fluorobenzoic acid (6.33 g, 74.3%).

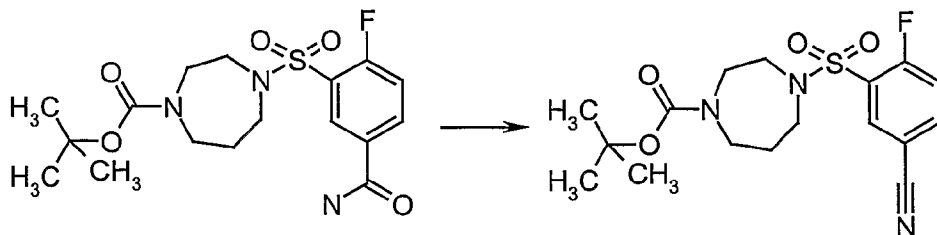
20



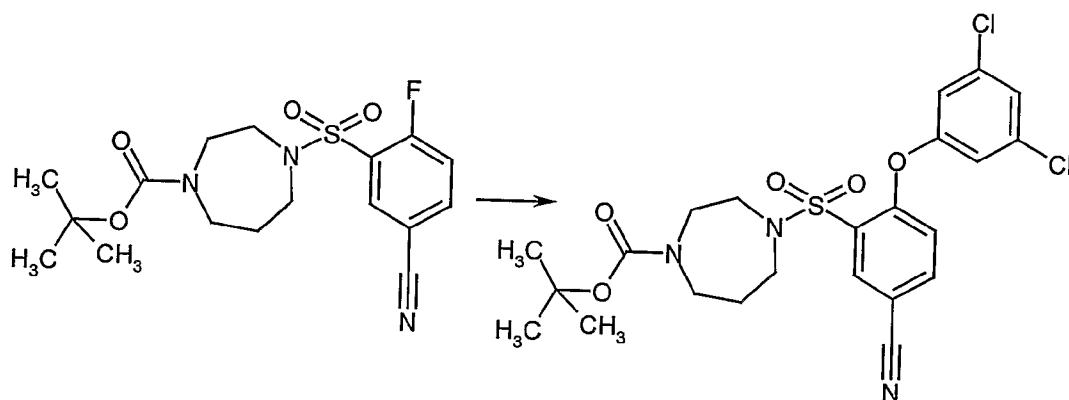
- (2) To a solution of 3-(chlorosulfonyl)-4-fluorobenzoic acid (1.0 g, 4.19 mmol) in THF (10 ml) was added *N*-*tert*-butyl 1-homopiperazinecarboxylate (0.92 g, 4.61 mmol) in THF (5 ml) dropwise at 0°C, followed by Et₃N (1.08 ml, 6.28 mmol). The mixture was stirred at room temperature for 6hrs. After quenched by water, the solvent was removed by evaporation. The resulting residue was dissolved in 1N NaOH (24 ml), and washed with Et₂O two times. Then the aqueous layer was acidified to pH 3-4 by 1N HCl, then extracted with EtOAc 3 times. The organic layer was dried over anhydrous Na₂SO₄, the solvent was evaporated in vacuo to give 3-{[4-(*tert*-butoxycarbonyl)-1,4-diazepan-1-yl]sulfonyl}-4-fluorobenzoic acid as a colorless form (1.12 g, 66.4%):



- (3) To a solution of 3-{[4-(*tert*-butoxycarbonyl)-1,4-diazepan-1-yl]sulfonyl}-4-fluorobenzoic acid (250 g, 0.62 mol) in THF (2000 ml) was added CDI (125 g, 0.77 mol) at 0°C under Ar. The mixture was stirred at 0°C for 1hr. Then NH₃ gas was bubbled into the mixture for 2 hrs. White precipitate was filtered off, and the filtrate was extracted with EtOAc, washed with 1N HCl, and sat. NaHCO₃ solution, and brine. The organic extracts were dried over anhydrous Na₂SO₄, the solvent was evaporated in vacuo to give *tert*-butyl 4-[[5-(aminocarbonyl)-2-fluorophenyl]sulfonyl]-1,4-diazepane-1-carboxylate as a white solid (240 g, 96.2%)

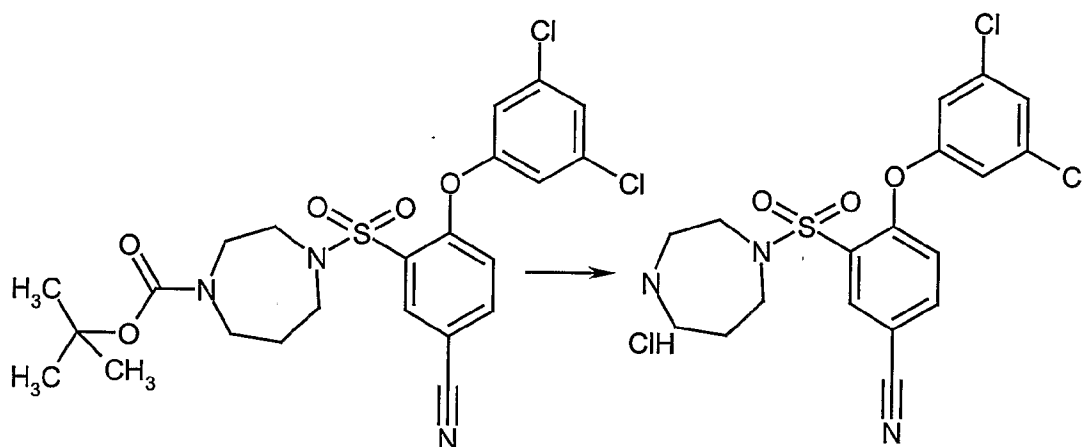


- (4) To a solution of *tert*-butyl 4-[[5-(aminocarbonyl)-2-fluorophenyl]sulfonyl]-1,4-diazepane-1-carboxylate (5.0 g, 12.5 mmol) in dry CH₂Cl₂ (150 ml) was added Et₃N (6.94 ml, 49.8 mmol) under Ar. Then the solution was cooled to -5°C (dry ice/*i*-PrOH). (CF₃SO₂)₂O (3.14 ml, 18.7 mmol) was added to the mixture dropwise, cooling under 5°C. After 1.5hrs, the reaction was quenched by water, then extracted with CH₂Cl₂, and washed with water and brine. The organic extract was dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica-gel (Hexane/EtoAc=1/1) to give *tert*-butyl 4-[(5-cyano-2-fluorophenyl)sulfonyl]-1,4-diazepane-1-carboxylate as a brown oil (4.12 g, 86.3%)



- (5) To a solution of *tert*-butyl 4-[(5-cyano-2-fluorophenyl)sulfonyl]-1,4-diazepane-1-carboxylate (4.12 g, 10.75 mmol) and 3,5-dichlorophenol (5.25 g, 32.2 mmol) in dioxane (100 ml) was added NaH (1.54 g, 37.6 mmol). The mixture was stirred under reflux for 1hr. After cooled to room temperature, the mixture was quenched by water, and extracted with CH₂Cl₂ and washed with 1N NaOH, and brine. The organic extract was dried over anhydrous Na₂SO₄, the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica-gel (Hexane/EtoAc=1/1) to give *tert*-butyl 4-[[5-cyano-2-(3,5-dichlorophenoxy)phenyl]sulfonyl]-1,4-diazepane-1-carboxylate as a white solid (3.08 g, 54.5%)

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- (6) To a solution of *tert*-butyl 4-{[5-cyano-2-(3,5-dichlorophenoxy)phenyl]-sulfonyl}-1,4-diazepane-1-carboxylate (3.1 g, 5.89 mmol) in CH₂Cl₂ (60 ml) was added 4N HCl in dioxane (60 ml). The mixture was stirred at room temperature for 2hrs. After the solvent was removed by evaporation, the resulting white solid was washed with CH₃CN to give 3-(1,4-diazepan-1-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile hydrochloride as a white solid (2.13 g, 78.2%); mp 278-280°C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.99-2.02 (2H, m), 3.19-3.24 (4H, m), 3.41-3.43 (2H, m), 3.64-3.66 (2H, m), 7.29 (1H, d, *J* = 8.5 Hz), 7.41 (2H, m), 7.59 (1H, m), 8.12 (1H, dd, *J* = 2.2, 8.8 Hz), 8.30 (1H, d, *J* = 1.9 Hz), 8.99 (1H, br); HPLC-MS (ESI): Calcd for C₁₈H₁₈Cl₃N₃O₃S [M+H]⁺ 426 and 428, found: 426 and 428.

15 Molecular weight: 462.785

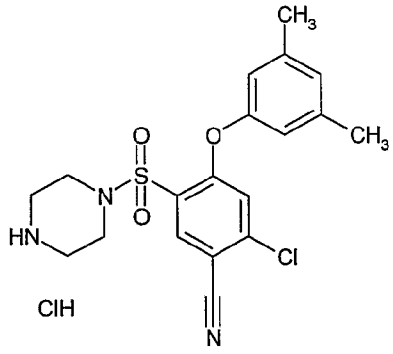
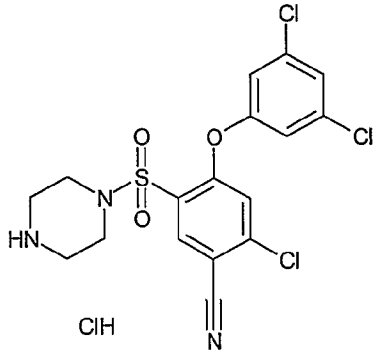
IC₅₀ (CCR3): 35 μM

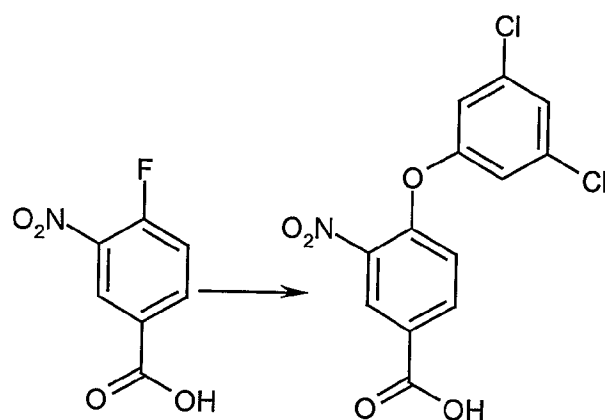
IC₅₀ (Ca²⁺): 20 μM

IC₅₀ (Chemotaxis): 8 μM

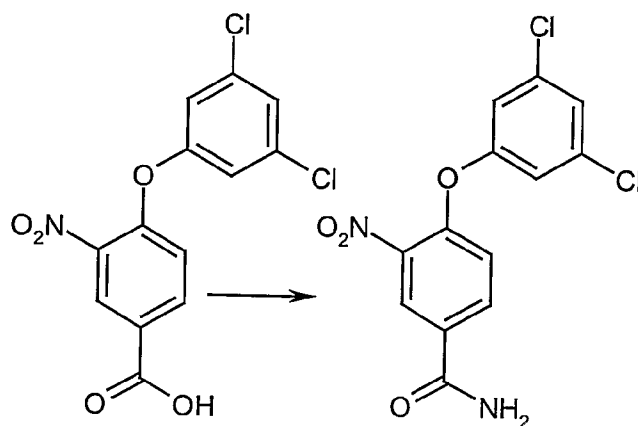
20 In the similar manner as described in Example 12-1 above, compounds in Example 12-2 and 12-3 as shown in Table 12 were synthesized.

Table 12

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
12-2	 ClH	442.36752	447	253		B
12-3	 ClH	483.2034	486	261		B

Example 13-1

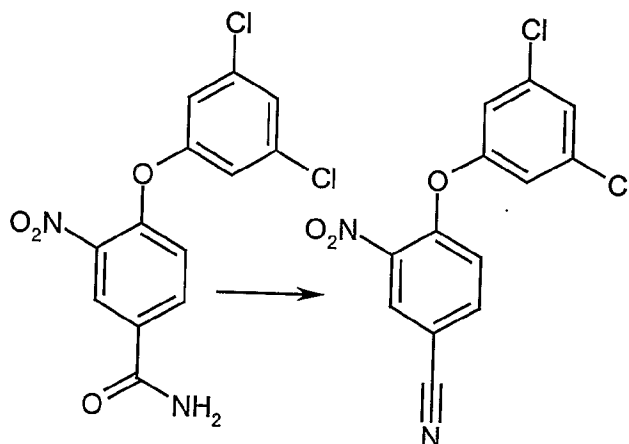
- 5 (1) To a mixture of 4-fluoro-3-nitrobenzoic acid (10.00 g, 54.02 mmol) and 3,5-dichlorophenol (13.21 g, 81.03 mmol) in THF (300 ml) was added NaH (5.40 g, 135.05 mmol) at room temperature. The resulting mixture was heated to 70°C. After 2 hrs, the reaction mixture was poured into water and 6N HCl (15ml) was added. The resulting mixture was extracted with EtOAc. The extract was washed with brine, and dried over MgSO₄, the solvent was
10 evaporated in vacuo. The residue was collected by filtration and washed with hexane to give 4-(3,5-dichlorophenoxy)-3-nitrobenzoic acid as a slight yellow powder (15.29 g 86.3%).



15

- (2) To a cooled solution of 4-(3,5-dichlorophenoxy)-3-nitrobenzoic acid (15.29 g, 46.60 mmol) in THF (300 ml), was added CDI (11.33 g, 69.90 mmol) and

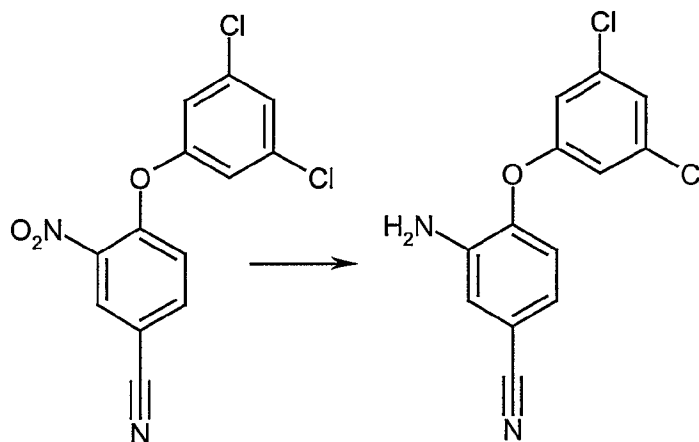
resulting mixture was allowed to warm to room temperature. After 2 hrs, the mixture was cooled with ice-bath and then NH_3 gas was introduced directly into the reaction mixture. After 2 hrs, the reaction mixture was condensed under reduce pressure. The residue was dissolved in water and the resulting mixture was extracted with EtOAc. The extract was washed with 1N NaOH, 1N HCl, and brine, dried over MgSO_4 . The solvent was evaporated in vacuo. The crude product was collected by filtration and washed with MeCN to give 4-(3,5-dichlorophenoxy)-3-nitrobenzamide as a white powder (15.72 g, quantitative).



- (3) The solution of 4-(3,5-dichlorophenoxy)-3-nitrobenzamide (15.50 g, 47.38 mmol) and $i\text{-Pr}_2\text{EtN}$ (49.52 ml, 284.30 mmol) in CH_2Cl_2 (500 ml) was cooled to -5°C with dry-ice/ $i\text{-PrOH}$ bath. Tf_2O (16.04 ml, 94.77 mmol) was added dropwise to the mixture below 0°C and then additional $i\text{-Pr}_2\text{EtN}$ (24.76 ml, 142.15 mmol) and Tf_2O (12.03 ml, 71.08 mmol) was added. The mixture was stirred at 0°C for 30 min. Water was added into the reaction mixture and the resulting mixture was condensed under reduced pressure. The obtained residue was partitioned between water and EtOAc and the resulting mixture was extracted with EtOAc. The extract was washed with 1N HCl and brine, dried over MgSO_4 . The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica-gel ($\text{CHCl}_3/\text{EtOAc}$

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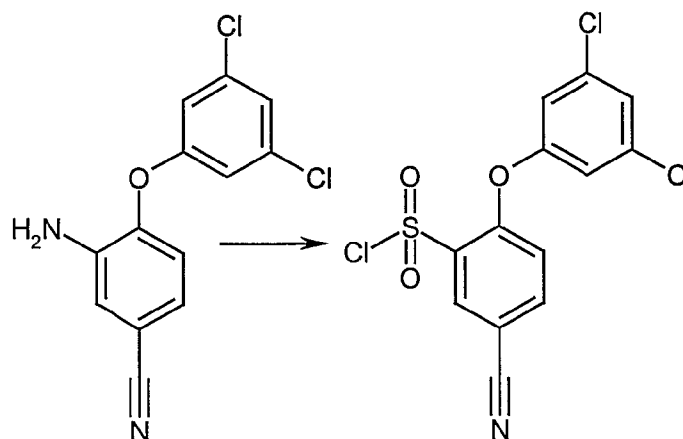
= 100/0 to 95/5) to give 5-cyano-2-(3,5-dichlorophenoxy)nitrobenzene as a white powder (4.08 g, 27.9 %).



5

- (4) The mixture of 5-cyano-2-(3,5-dichlorophenoxy)nitrobenzene (4.08 g, 13.20 mmol) and Tin(II) chloride dihydrate (17.87 g, 79.20 mmol) in EtOAc (200 ml) was heated to reflux for 3hrs. After cooled to room temperature, the reaction mixture was poured into sat. NaHCO₃. The mixture was extracted with EtOAc. The extract was washed with brine, and dried over MgSO₄. The solvent was evaporated in vacuo to give 5-cyano-2-(3,5-dichlorophenoxy)aniline (3.53 g, 95.8 %).

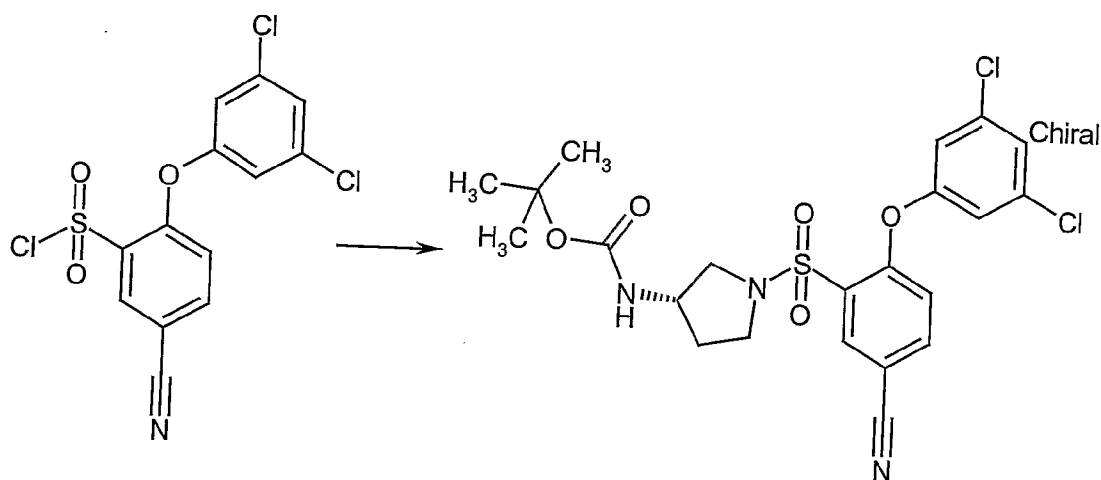
10



15

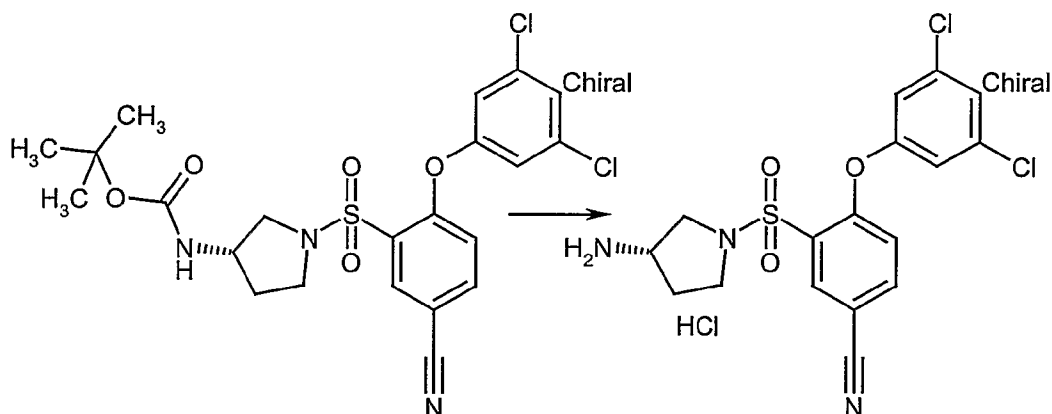
- 142 -

- (5) 5-Cyano-2-(3,5-dichlorophenoxy)aniline (3.53 g, 12.65 mmol) was dissolved in the mixture of conc. HCl (6.33 ml) and AcOH 2.53 ml). The solution was cooled to 0°C and sodium nitrite (0.96 g, 13.91 mmol) in water (1.27 ml) was added dropwise with stirring. After 30 min, the reaction mixture was added dropwise to the suspended mixture of CuCl (0.63 g, 6.32 mmol) in saturated solution of SO₂ in AcOH (25.32 ml) at 5°C. The reaction mixture was stirred at 10°C for 30 min, poured into water and the resulting mixture was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. The solvent was evaporated in vacuo to give 5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride as a brown powder (4.45 g, 97 %).



- (6) To a solution of 5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride (0.03 g 0.08 mmol) in THF (1 ml), (3S)-(tert-butoxycarbonylamino)pyrrolidine (0.05 g, 0.25 mmol) was added. The reaction mixture was stirred at room temperature overnight, then poured into water and the resulting mixture was extracted with EtOAc. The extract was washed with brine, and dried over MgSO₄. The solvent was evaporated in vacuo. The residue was purified by preparative TLC on silica gel (CH₂Cl₂/CH₃OH = 25/1) to give 1-{5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl}-(3S)-(tert-butoxycarbonylamino)pyrrolidine as an oil (0.02 g, 47%).

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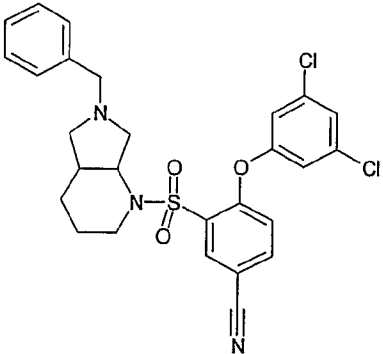
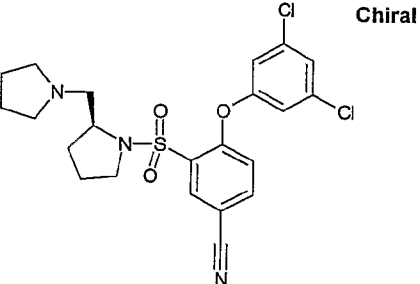
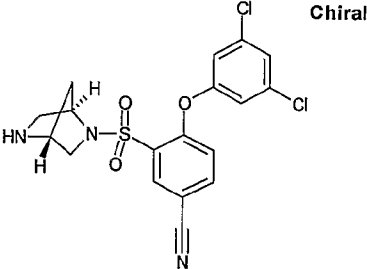
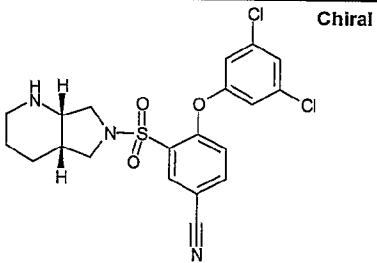
- (7) To the solution of 1-{5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl}-(3S)-
 (tert-butoxycarbonylamino)pyrrolidine (0.03 g, 0.04 mmol) in 1,4-dioxane
 5 (1 ml) was added 4N HCl (1 ml) in 1,4-dioxane. The reaction mixture was
 stirred at room temperature overnight. The solvent was evaporated in vacuo.
 The obtained residue was dissolved in THF followed by addition of ether. The
 produced precipitate was collected by filtration, washed with ether and dried
 in vacuo to give 1-{5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl}-(3S)-
 10 aminopyrrolidine hydrochloride as a white powder (13.4 mg, 77%); mp 276°C;
¹H NMR (500 MHz, DMSO-d₆) δ 1.92-1.97 (1H, m), 2.15-2.22 (1H, m),
 3.34-3.41 (2H, m), 3.51-3.56 (1H, m), 3.63-3.67 (1H, m), 3.79-3.83 (1H, m),
 7.34 (1H, d, *J* = 8.8 Hz), 7.39 (2H, dd, *J* = 1.6, 1.9 Hz), 8.13 (1H, dd, *J* = 8.5,
 2.2 Hz), 8.21 (3H, br), 8.29 (1H, d, *J* = 1.9); HPLC-MS (ESI): calcd for
 15 C₁₇H₁₅Cl₂N₃O₃S [M+H]⁺ 411 and 413, Found: 411 and 413.

Molecular weight: 448.758

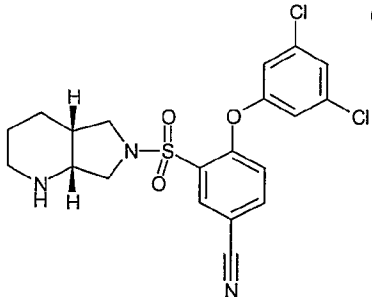
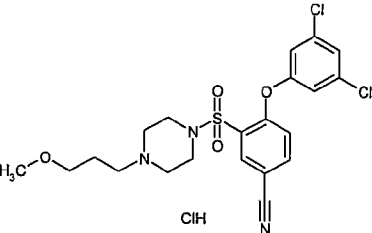
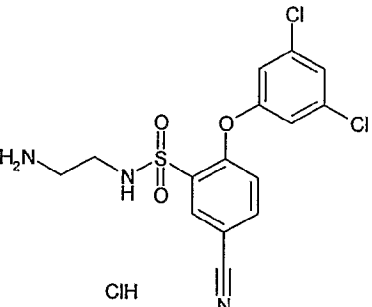
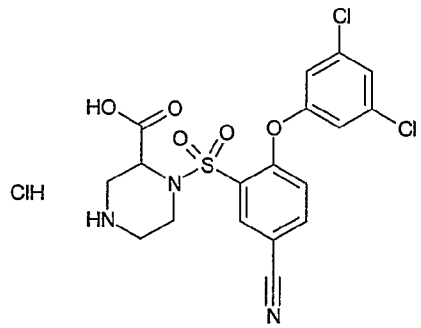
Activity grade Ca²⁺: A

- 20 In the similar manner as described in Example 13-1 above, compounds in Example
 13-2 to 13-12 as shown in Table 13 were synthesized.

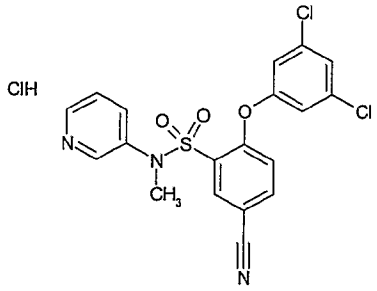
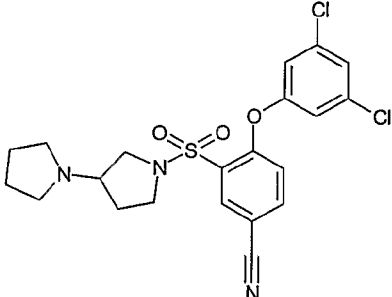
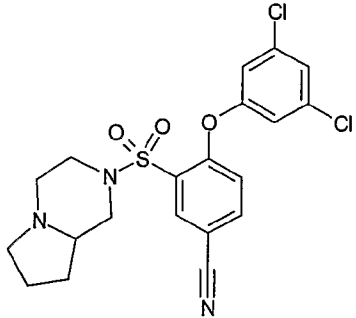
Table 13

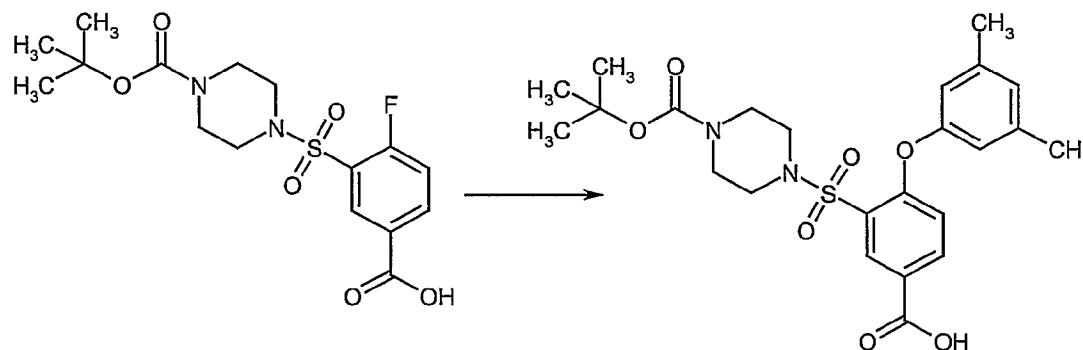
EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
13-2		542.4886	542	90-93	B	B
13-3		480.41691	480	144-145		A
13-4		424.30855	424	311-312	A	A
13-5		452.36273	452	163-165	B	A

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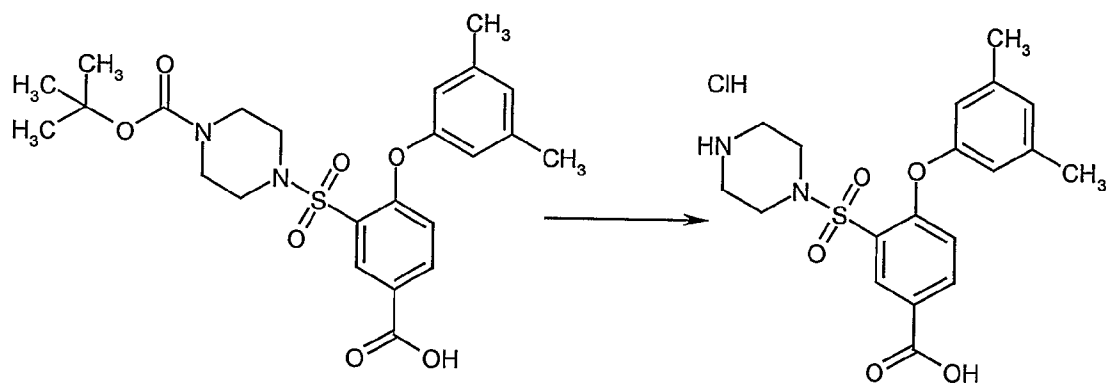
13-6	 <p>Chiral</p>	452.36273	452	164-165	30	40+G9
13-7	 <p>ClH</p>	520.86613	483	240	A	A
13-8	 <p>ClH</p>	422.72013	426	214		A
13-9	 <p>ClH</p>	492.76832	457	262	7	12+G12

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13-10	 <chem>CN(S(=O)(=O)c1ccc(C#N)cc1Oc2cc(Cl)cc(Cl)c2)c3ccncc3</chem>	470.76473	434	104		A
13-11	 <chem>C1CCN(C1)S(=O)(=O)c2ccc(C#N)cc2Oc3cc(Cl)cc(Cl)c3N4CCCC4</chem>	466.38982	467		13	8
13-12	 <chem>C1CCN(C1)S(=O)(=O)c2ccc(C#N)cc2Oc3cc(Cl)cc(Cl)c3N4CCCC4</chem>	452.36273	452	161	A	

Example 14-1

- 5 (1) To a cold (10°C) solution of 3-{[4-(tert-butoxycarbonyl)-1-piperazinyl]-sulfonyl}-4-fluorobenzoic acid (0.200 g, 0.515 mmol) and 3,5-dimethylphenol (0.063 g, 0.515 mmol) in 1,4-dioxane (1.0 ml) was added NaH (0.041 g, 1.030 mmol), and the stirring was continued for 15 min. The mixture was heated at 120°C for 3 hrs. N-Methyl-2-pyrrolidone (1.0 ml) was
- 10 added to the mixture, which was then heated at 120°C overnight. After cooled to room temperature, the mixture was quenched with water and then extracted with a 1:1 mixture of EtOAc and hexane. The aqueous phase was separated, and the organic phase was extracted with water. The combined aqueous phase was acidified to pH 3-4 with 1N HCl, and then extracted with EtOAc. The
- 15 separated organic phase was washed with water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was suspended in boiled MeOH for 1 h. After cooling to room temperature, the precipitate was collected by filtration, washed with MeOH and dried in vacuo to give 3-{[4-(tert-butoxycarbonyl)-1-piperazinyl]sulfonyl}-4-(3,5-dimethylphenoxy)-
- 20 benzoic acid (0.101 g, 40.0%): HPLC-MS (ESI): Calcd for C₂₄H₃₀N₂O₇S [M + H]⁺ 491, Found: 391(-Boc)



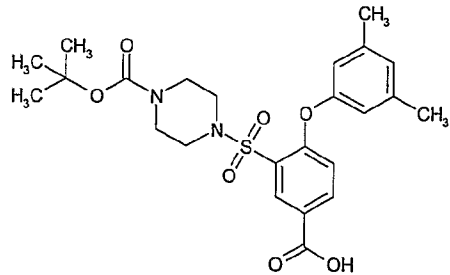
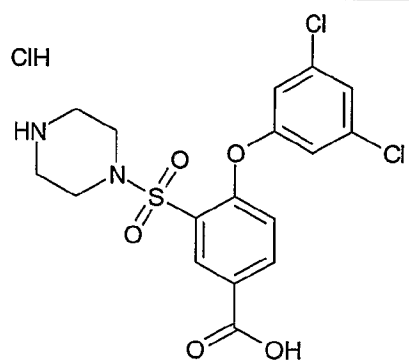
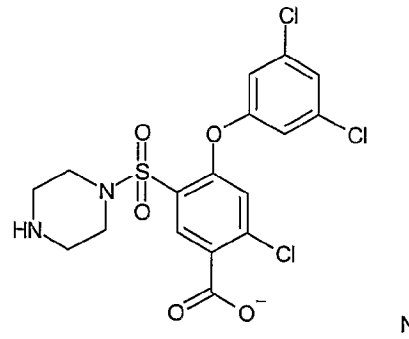
- (2) To a solution of 3-[[4-(tert-butoxycarbonyl)-1-piperazinyl]sulfonyl]-4-(3,5-dimethylphenoxy)benzoic acid (0.030 g, 0.061 mmol) in 1,4-dioxane (0.5 ml) was added 4N HCl in 1,4-dioxane (1.5 ml). The mixture was further stirred at room temperature for 3 hrs, and then concentrated in vacuo. The residue was washed twice with CH₃CN and dried in vacuo to give 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzoic acid hydrochloride (0.027 g, quantitative): ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.31 (6H, s), 3.17 (4H, br), 3.47 (4H, br), 6.87 (1H, s), 6.96 (1H, s), 6.98 (1H, br), 8.15 (1H, dd, *J* = 2.2, 8.8 Hz), 8.39 (1H, d, *J* = 2.2 Hz), 9.19 (1H, br), 13.36 (1H, br); HPLC-MS (ESI): Calcd for C₁₉H₂₂N₂O₅S [M + H]⁺ 391, Found: 391.

Molecular weight: 426.922

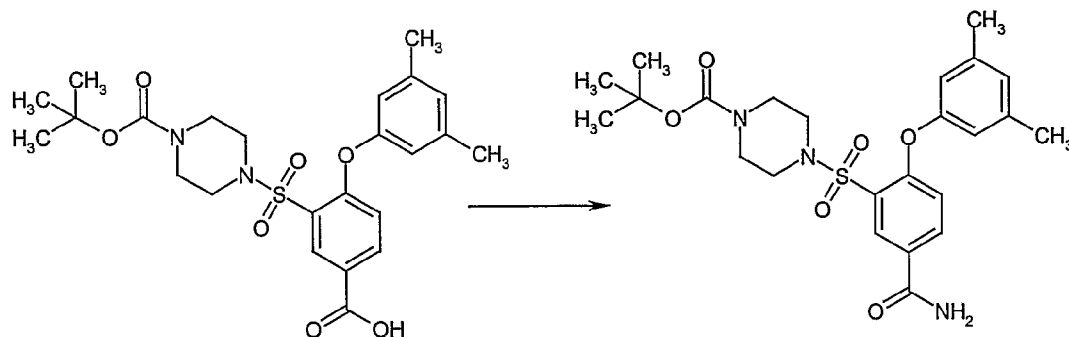
Activity grade Ca²⁺:A

In the similar manner as described in Example 14-1 above, compounds in Example 14-2 to 14-4 as shown in Table 14 were synthesized.

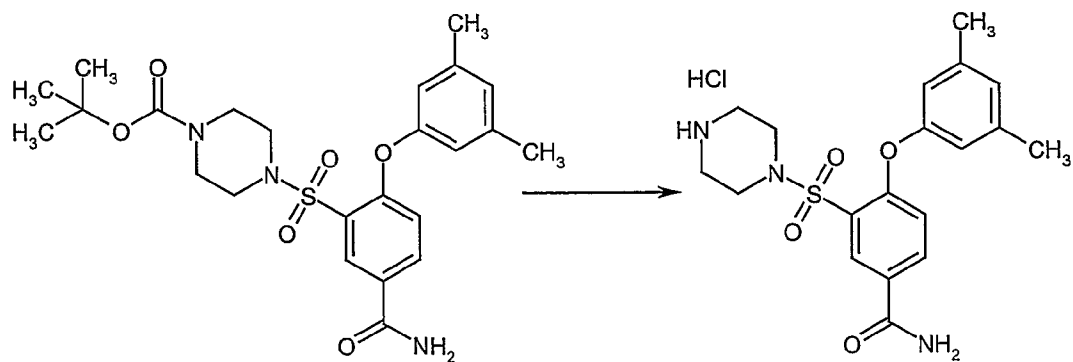
Table 14

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
14-2		490.5799	391	222		A
14-3		467.75844	431	>260		A
14-4	 Na ⁺	487.72433	466	307		B

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Example 15-1

- 5 (1) To a solution of 3-[[4-(tert-butoxycarbonyl)-1-piperazinyl]sulfonyl]-4-(3,5-dimethylphenoxy)benzoic acid (0.100 g, 0.204 mmol) in THF (1.0 ml) was added 1,1'-carbonylimidazole (0.041 g, 0.255 mmol), and the mixture was stirred at room temperature. After 3 hrs, 0.5M NH₃ in 1,4-dioxane was added, and the stirring was continued overnight. The resultant mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and saturated NaHCO₃. The separated organic phase was washed with water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The solid obtained was washed with EtOH and dried in vacuo to give *tert*-butyl 4-[[5-(aminocarbonyl)-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (0.071 g, 71.1%).
- 10
- 15



- 20 (2) To a suspension of *tert*-butyl 4-[[5-(aminocarbonyl)-2-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (0.057 g, 0.116 mmol) in 1,4-dioxane

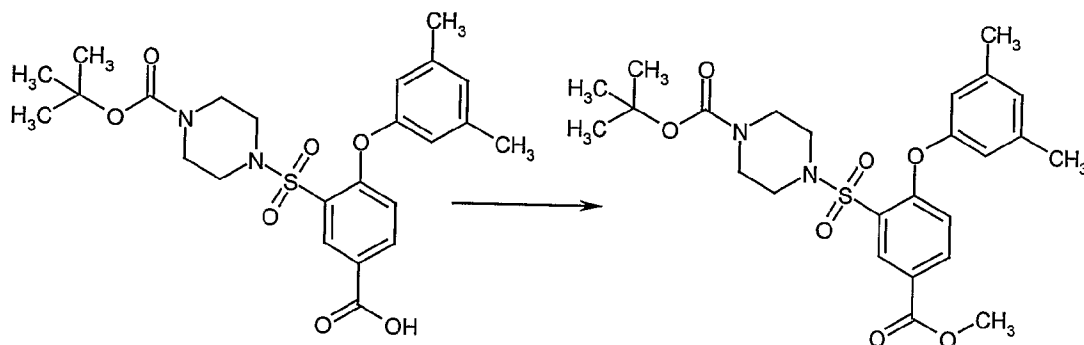
(1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml), and the mixture was stirred at room temperature for 2 hrs. The mixture was concentrated in vacuo, washed twice with CH₃CN and dried in vacuo to give 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzamide hydrochloride (0.047 g, 94.8%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.30 (6H, s), 3.16 (4H, br), 3.45 (4H, br), 6.83 (1H, s), 6.94 (1H, s), 6.95 (1H, d, *J* = 8.8 Hz), 7.51 (1H, s), 8.11 (1H, dd, *J* = 2.2, 8.5 Hz), 8.18 (1H, s), 8.37 (1H, d, *J* = 2.2 Hz), 9.22 (2H, s); HPLC-MS (ESI): Calcd for C₁₉H₂₃N₃O₄S [M + H]⁺ 390, Found: 390.

Molecular weight: 425.937

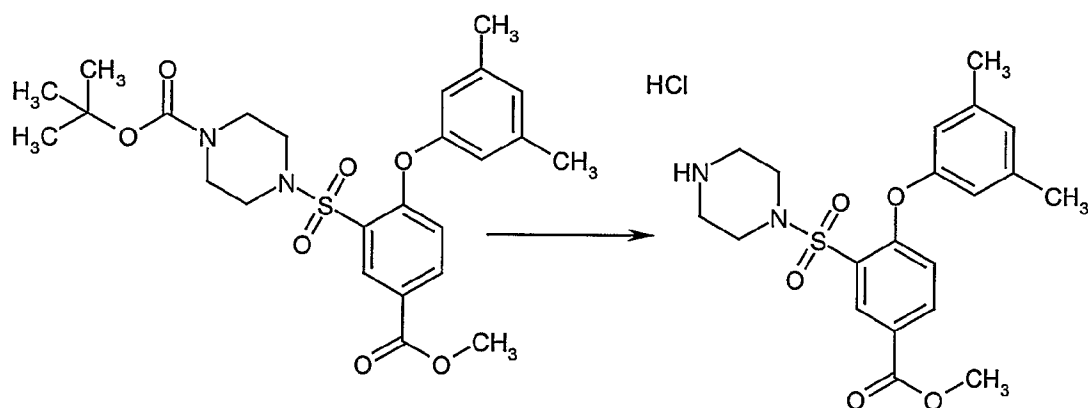
Activity grade RBA:

Activity grade Ca²⁺:A

Example 15-2



- (1) To a mixture of 3-[[4-(tert-butoxycarbonyl)-1-piperazinyl]sulfonyl]-4-(3,5-dimethylphenoxy)benzoic acid (0.300 g, 0.612 mmol), K₂CO₃ (0.169 g, 1.223 mmol) and DMF (3.0 ml) was added MeI (0.174 g, 1.223 mmol), and the stirring was continued at room temperature overnight. The mixture was quenched with water, and extracted with EtOAc. The separated organic phase was washed with water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was recrystallized from MeOH to give tert-butyl 4-[[2-(3,5-dimethylphenoxy)-5-(methoxycarbonyl)phenyl]sulfonyl]-1-piperazinecarboxylate (0.276 g, 89%).



- (2) To a suspension of tert-butyl 4-{[2-(3,5-dimethylphenoxy)-5-(methoxycarbonyl)phenyl]sulfonyl}-1-piperazinecarboxylate (0.030 g, 0.059 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The resulting clear solution was stirred at room temperature for 3 hrs. The mixture was concentrated in vacuo, washed twice with Et₂O and dried in vacuo to give methyl 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzoate hydrochloride (0.027 g, quantitative): mp 120°C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.31 (6H, s), 3.16 (4H, br), 3.48 (4H, br), 3.88 (3H, s), 6.89 (2H, s), 6.97 (1H, d, *J* = 2.3 Hz), 6.98 (1H, s), 8.17 (2H, dd, *J* = 2.3, 9.0 Hz), 8.40 (1H, d, *J* = 2.3 Hz), 9.22 (2H, br); HPLC-MS (ESI): Calcd for C₂₀H₂₄N₂O₅S [M + H]⁺ 405, Found: 405.

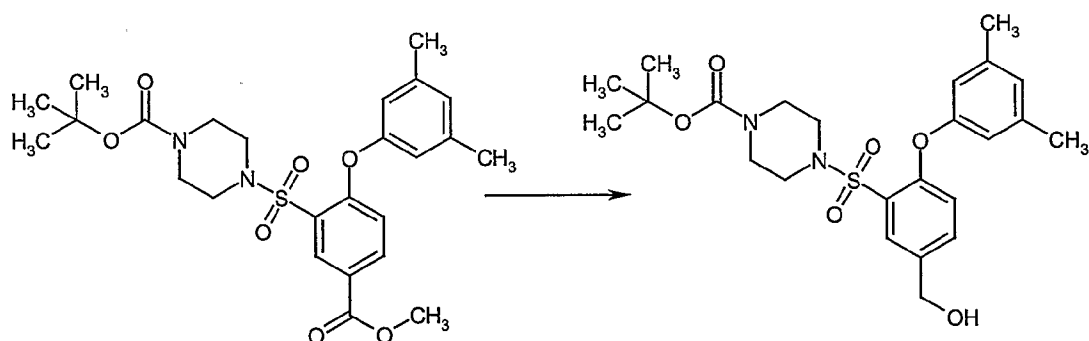
Molecular weight: 440.949

Activity grade Ca²⁺:A

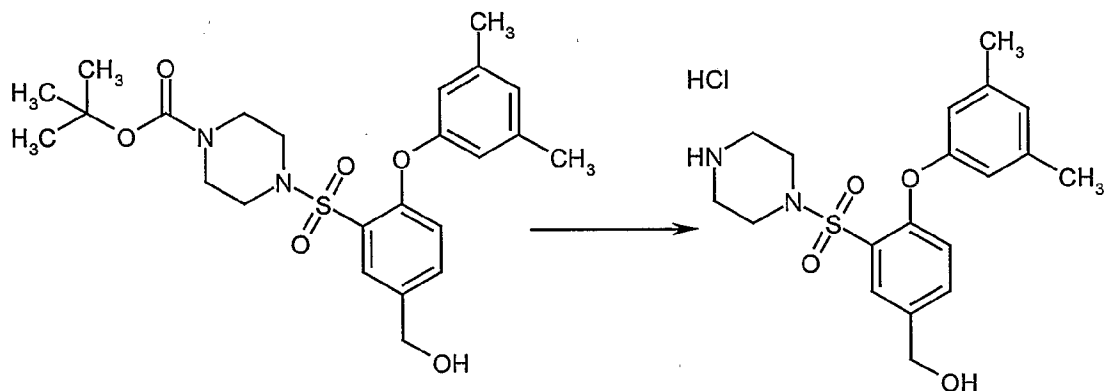
In the similar manner as described in Example 15-1 or 15-2 above, compounds in Example 15-3 and 15-4 as shown in Table 15 were synthesized.

Table 15

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
15-3	 <chem>CC1=CC(=CC(=C1)OC2=CC(=CC(=C2)C(=O)N)Cl)S(=O)(=O)N3CCCCC3</chem> ClH	460.38286	424	161		B
15-4	 <chem>ClC1=CC(=CC(=C1)OC2=CC(=CC(=C2)C(=O)N)F)S(=O)(=O)N3CCCCC3</chem> ClH	484.76414	488	>300		B

Example 16-1

- (1) To a cold (0°C) solution of 4-{[2-(3,5-dimethylphenoxy)-5-(methoxycarbonyl)phenyl]sulfonyl}-1-piperazinecarboxylate (0.227 g, 0.450 mmol) in THF (3.0 ml) was added LiBH₄ (0.012 g, 0.540 mmol). The mixture was stirred at room temperature for 3 hrs, and at 60°C for 4 hrs. After cooled to room temperature, the mixture was quenched with saturated NH₄Cl, and extracted with EtOAc. The separated organic phase was washed with water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was purified by recrystallization from CH₃CN to give tert-butyl 4-{[2-(3,5-dimethylphenoxy)-5-(hydroxymethyl)phenyl]sulfonyl}-1-piperazinecarboxylate (0.156 g, 72.8%).



- (2) To a solution of tert-butyl 4-{[2-(3,5-dimethylphenoxy)-5-(hydroxymethyl)phenyl]sulfonyl}-1-piperazinecarboxylate (0.027 g, 0.057 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture was stirred at room temperature for 3 hrs. The mixture was concentrated in vacuo,

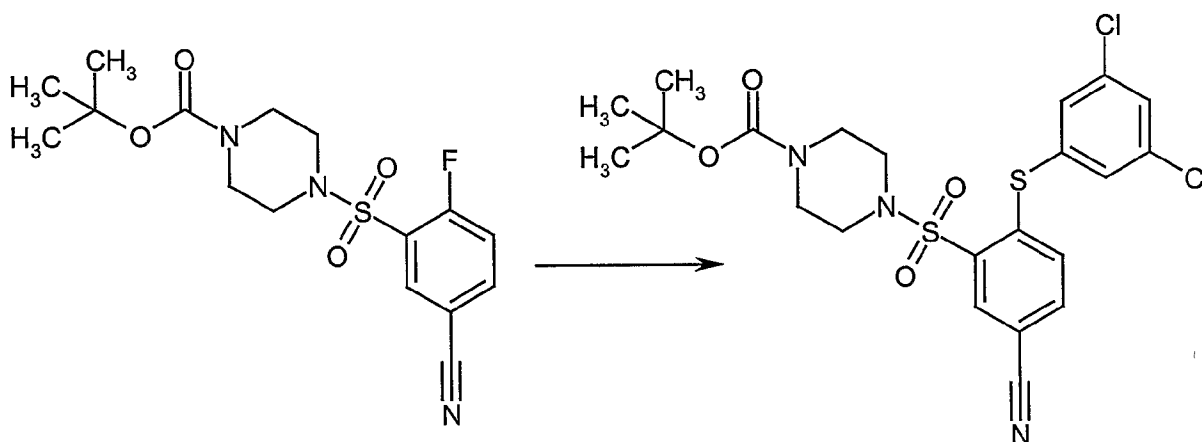
- 155 -

washed twice with Et₂O and dried in vacuo to give [4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)phenyl]methanol hydrochloride (0.020 g, 85.5%): mp 160°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.27 (6H, s), 3.14 (4H, br), 3.39 (4H, br), 4.53 (2H, d, *J* = 5.7 Hz), 5.42 (1H, t, *J* = 5.7 Hz), 6.71 (2H, s), 6.86 (1H, s), 6.96 (1H, d, *J* = 8.5 Hz), 7.57 (1H, dd, *J* = 2.2, 8.5 Hz), 7.83 (1H, d, *J* = 1.9 Hz), 9.12 (2H, br); HPLC-MS (ESI): Calcd for C₁₉H₂₄N₂O₄S [M + H]⁺ 377, Found: 377.

Molecular weight: 412.939

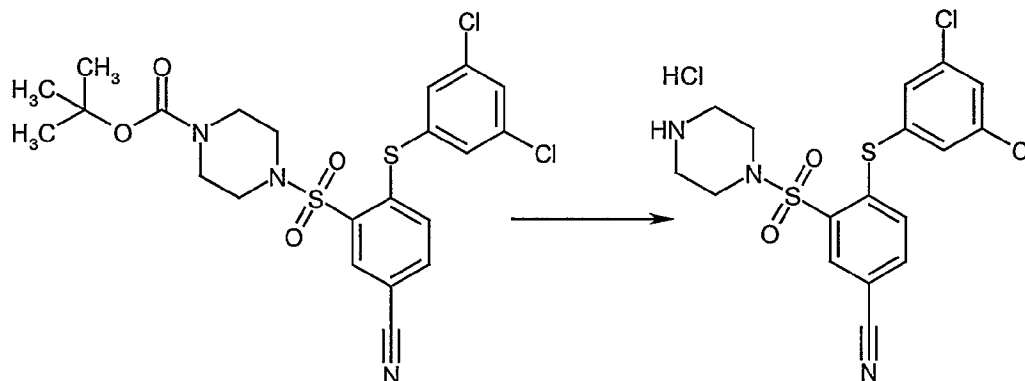
Activity grade Ca²⁺:A

Example 17-1



- (1) To a stirred suspension of NaH (60%, 0.015 g, 0.375 mmol) in 1,4-dioxane (2.0 ml) was added 3,5-dichlorothiophenol (0.067 g, 0.374 mmol). After 15 min, tert-butyl 4-[(5-cyano-2-fluorophenyl)sulfonyl]-1-piperazinecarboxylate (0.100 g, 0.271 mmol) was added, and the suspension was stirred at room temperature for 10 min. THF (0.5 ml) was added, and the stirring was continued for 2 hrs. The mixture was quenched with water, and extracted with EtOAc and saturated aqueous NaHCO₃ solution. The separated organic phase was washed with water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was recrystallized from CH₃CN to give tert-

tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)sulfanyl]phenyl}sulfonyl)-1-piperazinecarboxylate (0.088 g, 61.5%).



- 5 (2) To a solution of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)sulfanyl]-phenyl}sulfonyl)-1-piperazinecarboxylate (0.020 g, 0.038 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml), and the stirring was continued for 3 hrs. The mixture was concentrated in vacuo. The residue was recrystallized from diisopropylether. The solid obtained was washed with
- 10 diisopropylether, dried in vacuo to give 4-[(3,5-dichlorophenyl)sulfanyl]-3-(1-piperazinylsulfonyl)benzonitrile hydrochloride (0.017 g, 96.6%): mp 82°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.19 (4H, br), 3.53 (4H, br), 7.18 (1H, d, *J* = 8.5 Hz), 7.73 (1H, d, *J* = 1.9 Hz), 7.87 (1H, t, *J* = 1.9 Hz), 7.97 (1H, dd, *J* = 1.3, 8.5 Hz), 8.3 (1H, d, *J* = 1.6 Hz), 8.99 (2H, br); HPLC-MS (ESI): Calcd for C₁₇H₁₅Cl₂N₃O₂S₂ [M + H]⁺ 428, Found: 428.
- 15

Molecular weight: 464.823

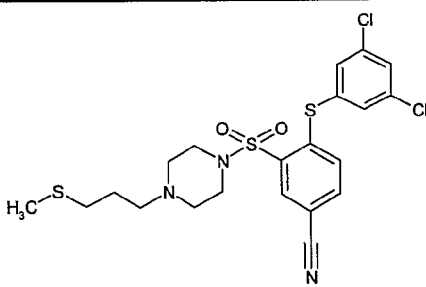
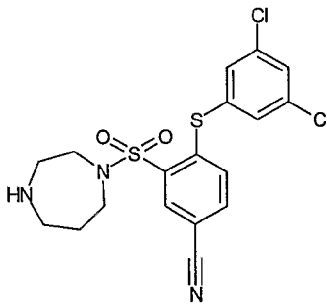
IC₅₀ (CCR3): 3 μM

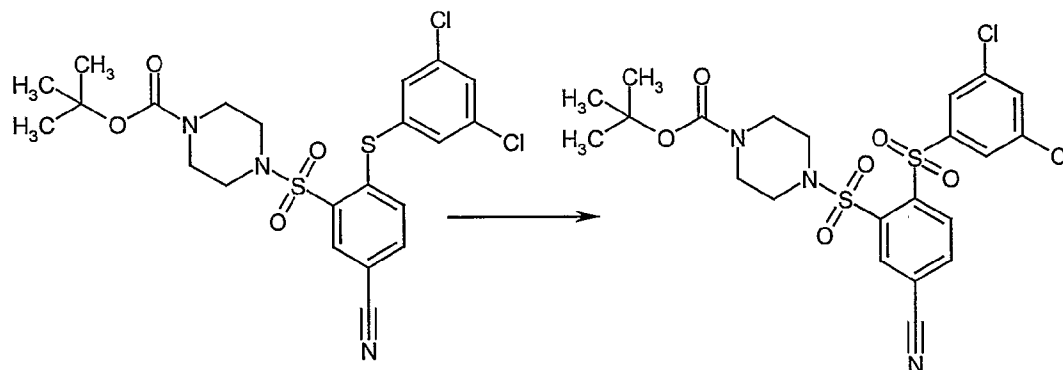
IC₅₀ (Ca²⁺): 2 μM

20 IC₅₀ (Chemotaxis): 2 μM

In the similar manner as described in Example 17-1 above, compounds in Example 17-2 and 17-3 as shown in Table 17 were synthesized.

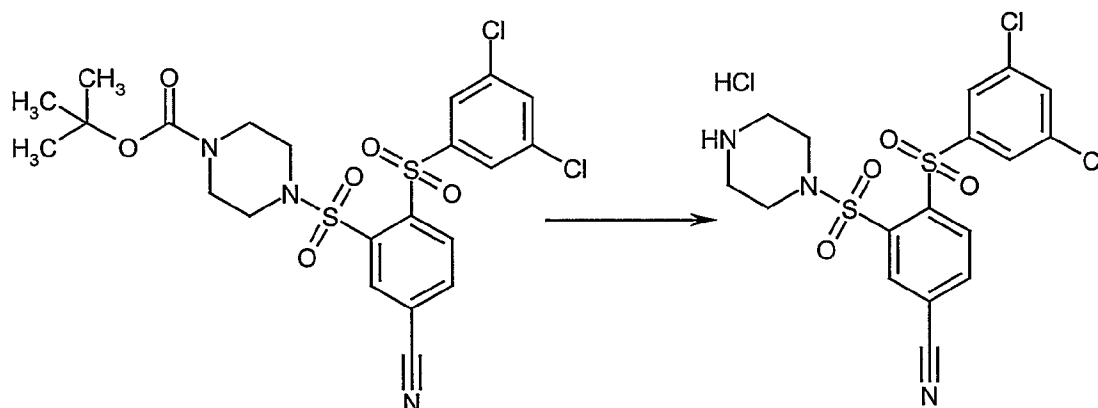
Table 17

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
17-2		516.53436	516	124		A
17-3	 ClH	478.85006	442	277-278	3	1

Example 18-1

- 5 (1) To a stirred mixture of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)-
sulfanyl]phenyl}sulfonyl)-1-piperazinecarboxylate (0.011 g, 0.020 mmol),
CCl₄ (0.4 ml), CH₃CN (0.4 ml) and water (0.8 ml) was added NaIO₄ (0.030 g,
0.142 mmol) followed by RuCl₃ (0.003 g, 0.014 mmol). The mixture was
stirred at room temperature for 4 hrs. The mixture was partitioned between
10 EtOAc and water. The separated organic phase was washed with saturated
aqueous NaHCO₃ solution and brine, dried over Na₂SO₄. The solvent was
evaporated in vacuo. The residue was dissolved in hot CH₃CN, and allowed
to cool to room temperature. The precipitate was collected by filtration,
washed with CH₃CN, and dried in vacuo to give tert-butyl 4-({5-cyano-2-
15 [(3,5-dichlorophenyl)sulfonyl]phenyl}sulfonyl)-1-piperazinecarboxylate
(0.016 g, 60.3%).

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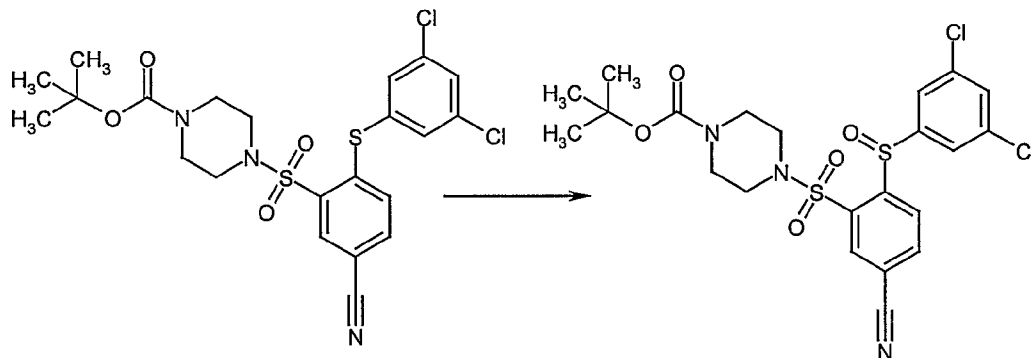


- (2) To a suspension of tert-butyl 4-((5-cyano-2-[(3,5-dichlorophenyl)sulfonyl]phenyl)sulfonyl)-1-piperazinecarboxylate (0.011 g) in 1,4-dioxane (0.5 ml) was added 4N HCl in 1,4-dioxane (1.5 ml), and the stirring was continued for 3 hrs. The mixture was concentrated in vacuo, and recrystallized with diisopropylether. The obtained solid was washed with diisopropylether, and dried in vacuo to give 4-[(3,5-dichlorophenyl)sulfonyl]-3-(1-piperazinylsulfonyl)benzonitrile hydrochloride (0.008 g, 82%): mp 258°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.15 (4H, br), 3.57 (4H, br), 7.94 (2H, d, *J* = 1.9 Hz), 8.05 (1H, t, *J* = 1.9 Hz), 8.52 - 8.55 (2H, m), 8.72 (1H, d, *J* = 8.5 Hz), 8.96 (2H, br); FAB-MS: Calcd for C₁₇H₁₅Cl₂N₃O₄S₂ [M + H]⁺ 460, Found: 460.

Molecular weight: 496.821

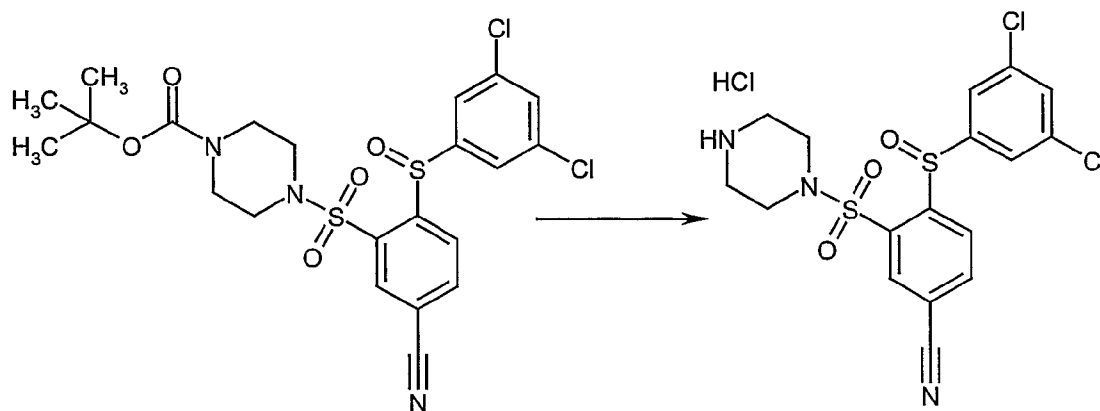
IC₅₀ (CCR3): 1,2 μM

IC₅₀ (Ca²⁺): 7 μM

Example 19-1

- 5 (1) To a cold (0°C) solution of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)-
sulfinyl]phenyl}sulfonyl)-1-piperazinecarboxylate (0.022 g, 0.042 mmol) in
CH₂Cl₂ (0.6 ml) was added m-chloroperbenzoic acid (0.022 g, 0.062 mmol),
and the stirring was continued for 1 h. The mixture was allowed to warm to
room temperature, and stirred for 30 min. The mixture was quenched with
10 Na₂SO₃ solution, and extracted with EtOAc. The extract was washed
with saturated NaHCO₃, water and brine, dried over Na₂SO₄. The solvent was
evaporated in vacuo. The solid obtained was washed twice with MeOH and
dried in vacuo to give tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)sulfinyl]-
phenyl}sulfonyl)-1-piperazinecarboxylate (0.022 g, 97.1%).

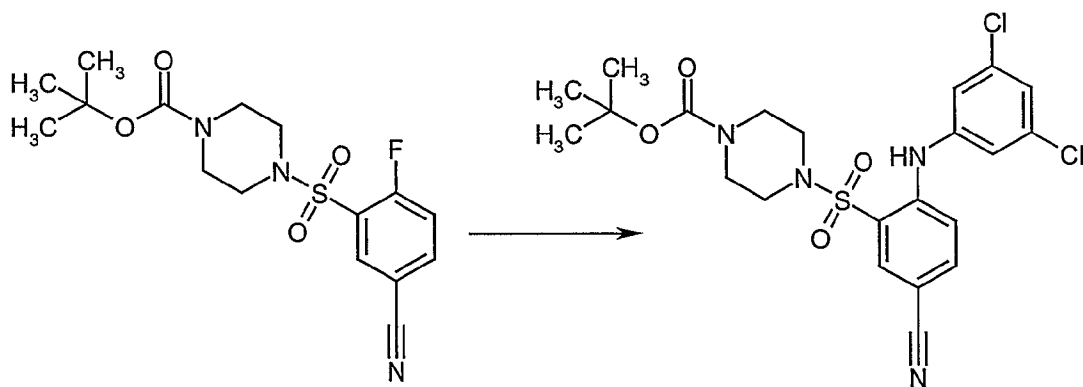
15



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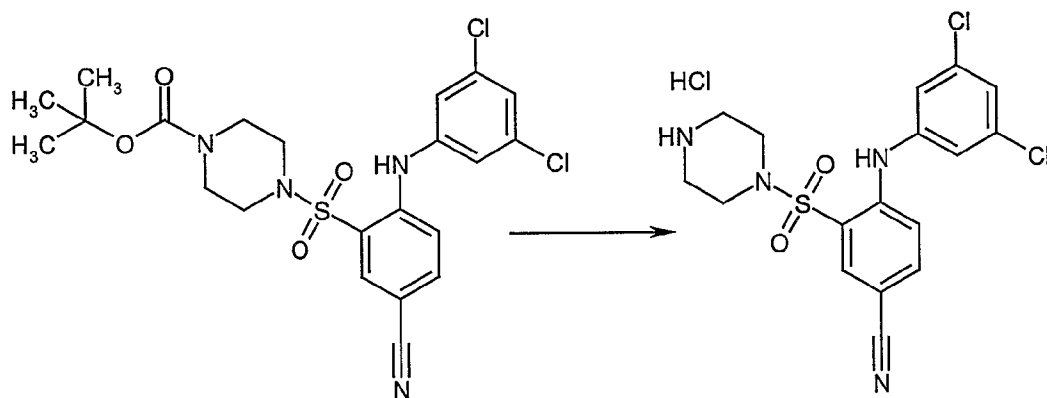
- (2) To a suspension of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)sulfinyl]-phenyl}sulfonyl)-1-piperazinecarboxylate (0.017 g, 0.031 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture was stirred at room temperature for 3 hrs, and then concentrated in vacuo. The residue was washed twice with CH₃CN, and dried in vacuo to give 4-[(3,5-dichlorophenyl)sulfinyl]-3-(1-piperazinylsulfonyl)benzonitrile hydrochloride (0.008 g, 53.3%): mp 219°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.20 - 3.24 (4H, m), 3.43 - 3.46 (4H, m), 7.74 (1H, d, *J* = 1.9 Hz), 7.85 (1H, t, *J* = 1.9 Hz), 8.42 (1H, d, *J* = 1.6 Hz), 8.47 (1H, dd, *J* = 1.6, 8.2 Hz), 8.52 (1H, d, *J* = 8.2 Hz), 8.87 (2H, br); FAB-MS: Calcd for C₁₇H₁₅Cl₂N₃O₃S₂ [M + H]⁺ 444, Found: 444.

Molecular weight: 480.822

Activity grade Ca²⁺:B**Example 20-1**

- (1) A solution of tert-butyl 4-[(5-cyano-2-fluorophenyl)sulfonyl]-1-piperazinecarboxylate (0.100 g, 0.271 mmol) in THF (2.0 ml) was cooled with a water bath, and KOtBu (0.033 g, 0.298 mmol) was added with stirring. The mixture was heated at reflux for 7 hrs. After cooled to room temperature, KOtBu (0.030 g, 0.267 mmol) was added, and the mixture was heated at reflux overnight. After cooled to room temperature, the mixture was quenched with

saturated NH_4Cl , and extracted with EtOAc. The separated organic phase was washed with water and brine, dried over Na_2SO_4 . The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (Hexane/ EtOAc=4/1). The product obtained was suspended in hexane including a small amount of EtOAc, collected by filtration, washed with hexane including a small amount of EtOAc, and dried in vacuo to give tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)amino]phenyl}sulfonyl)-1-piperazinecarboxylate (0.087 g, 62.8%).

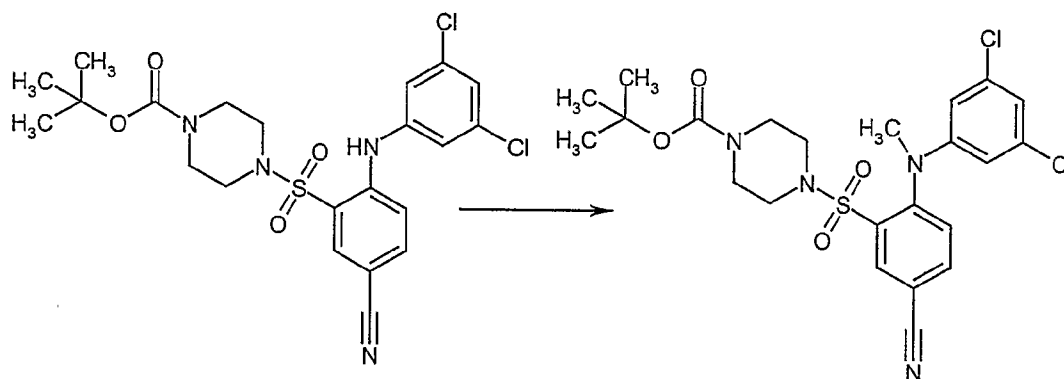


- (2) To a solution of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)amino]phenyl}sulfonyl)-1-piperazinecarboxylate (0.035 g, 0.068 mmol) in 1,4-dioxane (0.5 ml) was added 4N HCl in 1,4-dioxane (1.5 ml), and the stirring was continued for 3 hrs. The mixture was concentrated in vacuo. The residue was crystallized from CH_3CN , washed with CH_3CN , and dried in vacuo to give 4-[(3,5-dichlorophenyl)amino]-3-(1-piperazinylsulfonyl)benzonitrile hydrochloride (0.030 g, 97.9%): ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 3.13 - 3.16 (4H, m), 3.34 - 3.37 (4H, m), 7.37 (1H, d, $J = 8.8$ Hz), 7.39 - 7.41 (1H, m), 7.41 (2H, s), 7.93 (1H, dd, $J = 2.2, 8.8$ Hz), 8.13 (1H, d, $J = 2.2$ Hz), 8.41 (1H, s), 8.87 (2H, br); FAB-MS: Calcd for $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 411, Found: 411.

- 163 -

Molecular weight: 447.773

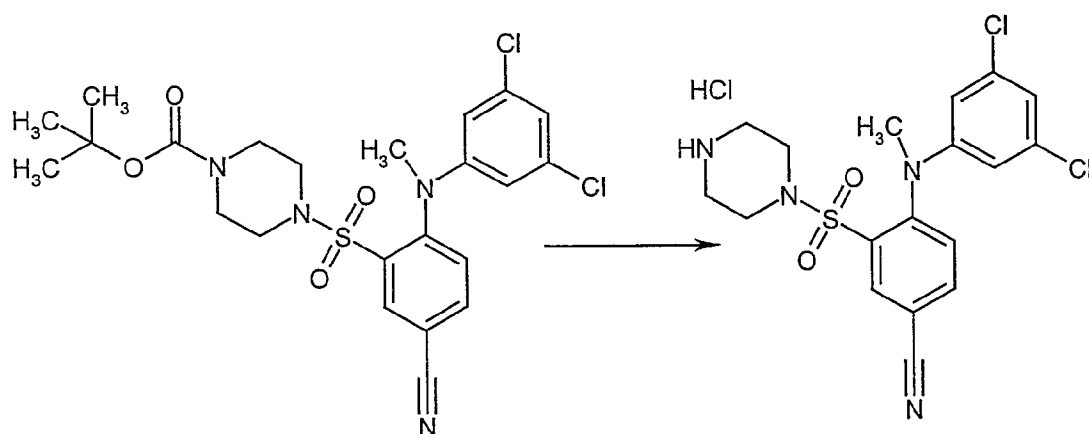
Activity grade RBA: A

Activity grade Ca²⁺: A5 **Example 21-1**

- (1) To a cold (0°C) solution of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)-
 10 amino]phenyl}sulfonyl)-1-piperazinecarboxylate (0.049 g, 0.096 mmol) in
 DMF (1.5 ml) including MeI (0.041 g, 0.287 mmol) was added NaH (0.005 g,
 0.115 mmol), and the stirring was continued for 1 h. The mixture was allowed
 to warm to room temperature, and the stirred was continued for 2 hrs. The
 mixture was cooled with ice-water bath, quenched with saturated NH₄Cl
 15 solution, and extracted with EtOAc and water. The separated organic phase
 was washed with brine, dried over Na₂SO₄. The solvent was evaporated in
 vacuo. The residue was purified by column chromatography on silica gel
 (Hexane/ EtOAc=4/1) to give tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)-
 (methyl)amino]phenyl}sulfonyl)-1-piperazinecarboxylate (0.048 g, 95.3%).

20

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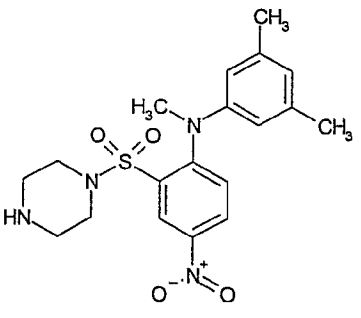


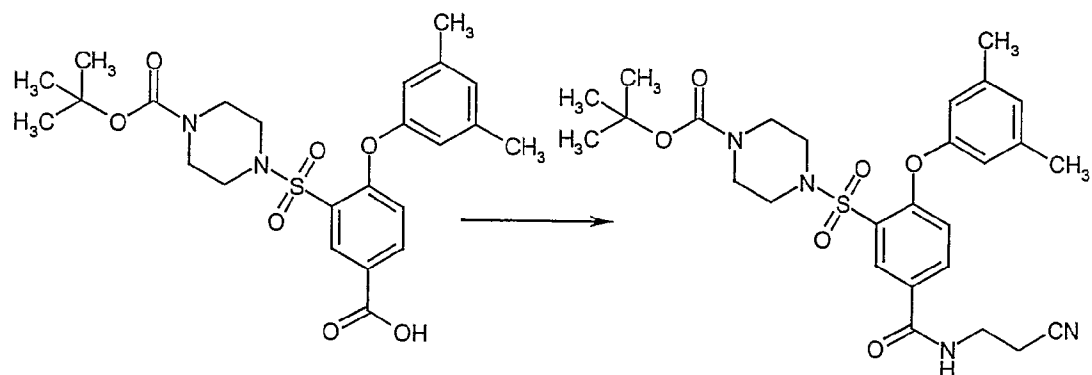
- (2) To a suspension of tert-butyl 4-({5-cyano-2-[(3,5-dichlorophenyl)(methyl)-
 amino]phenyl}sulfonyl)-1-piperazinecarboxylate (0.043 g, 0.082 mmol) in
 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture
 was stirred at room temperature for 2 hrs, and then concentrated in vacuo. The
 residue was washed twice with Et₂O, and dried in vacuo to give 4-[(3,5-
 dichlorophenyl)(methyl)amino]-3-(1-piperazinylsulfonyl)benzonitrile hydro-
 chloride (0.037 g, 97.9%): mp 163°C¹H NMR (500 MHz, DMSO-*d*₆) δ 2.98
 (4H, br), 3.18 (3H, s), 3.29 (4H, br), 6.53 (2H, d, *J* = 1.6 Hz), 6.97 (1H, t, *J* =
 1.6 Hz), 7.71 (1H, d, *J* = 8.2 Hz), 8.31 (1H, dd, *J* = 2.2, 8.2 Hz), 8.39 (1H, d,
J = 1.9 Hz), 8.92 (2H, br); FAB-MS: Calcd for C₁₈H₁₈Cl₂N₄O₂S [M + H]⁺
 425, Found:

Molecular weight: 461.800
 Activity grade Ca²⁺:B

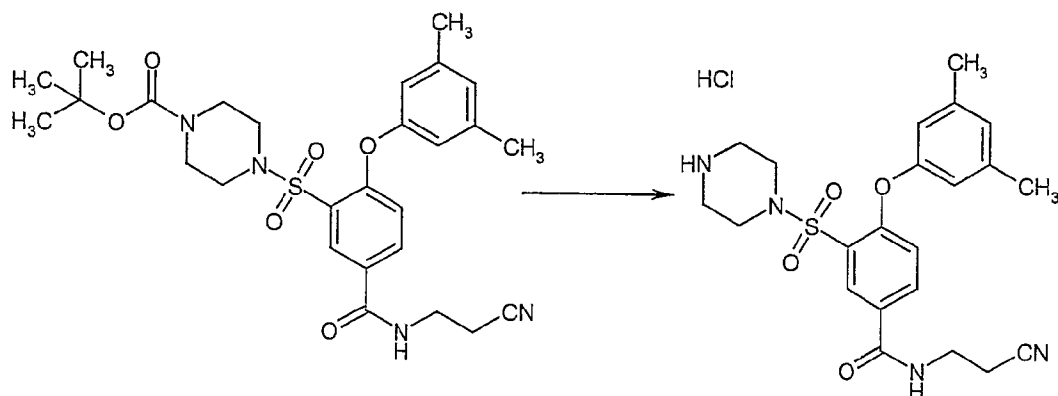
In the similar manner as described in Example 21-1 above, compounds in Example
 21-2 as shown in Table 21 were synthesized.

Table 21

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
21-2	 ClH	440.9525	405	243		A

Example 22-1

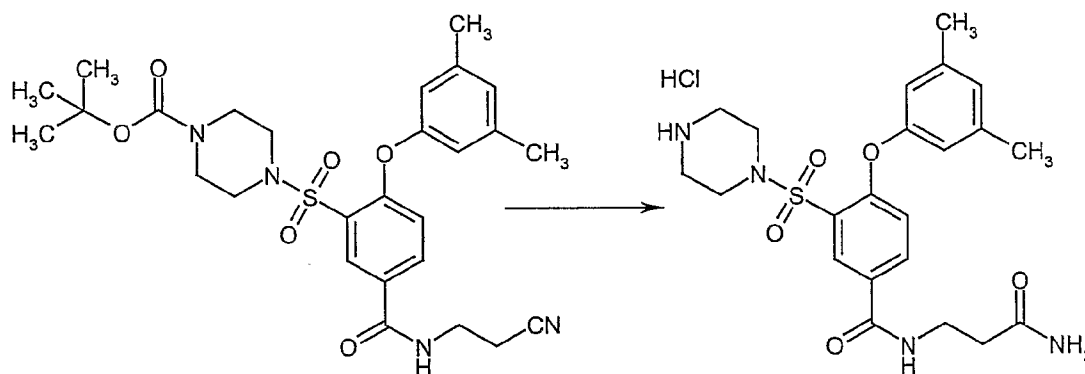
- 5 (1) To a cold (0°C) mixture of 3-[[4-(tert-butoxycarbonyl)-1-piperazinyl]sulfonyl]-4-(3,5-dimethylphenoxy)benzoic acid (0.450 g, 0.917 mmol), 3-amino-
propionitrile (0.072 g, 1.009 mmol), HOBt (0.186 g, 1.376 mmol) and DMF
10 (5.0 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydro-
chloride (0.211 g, 1.101 mmol). After 15 min, the mixture was allowed to
warm to room temperature, and the stirring was continued overnight. The
mixture was partitioned between EtOAc and water. The separated organic
phase was washed with saturated NaHCO₃ solution, water and brine, dried
over Na₂SO₄. The solvent was evaporated in vacuo. The residue was purified
15 by column chromatography on silica gel (Hexane/ EtOAc=1/2) to give tert-
butyl 4-[[5-[[[(2-cyanoethyl)amino]carbonyl]-2-(3,5-dimethylphenoxy)phen-
yl]sulfonyl]-1-piperazinecarboxylate (0.490 g, 98.4%).



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- (2) To a solution of tert-butyl 4-{[5-{[(2-cyanoethyl)amino]carbonyl}-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (0.030 g, 0.055 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture was stirred at room temperature for 1.5 hrs, and then concentrated in vacuo. The residue was crystallized from Et₂O, washed with Et₂O and dried in vacuo to give N-(2-cyanoethyl)-4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzamide hydrochloride (0.025 g, 94.4%): mp 101°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.30 (6H, s), 2.79 (2H, t, *J* = 6.4 Hz), 3.14 - 3.18 (4H, m), 3.42 - 3.45 (4H, m), 3.47 - 3.54 (2H, m), 6.82 (2H, s), 6.95 (1H, s), 7.02 (1H, d, *J* = 8.7 Hz), 8.10 (1H, dd, *J* = 2.3, 8.7 Hz), 8.38 (1H, d, *J* = 2.3 Hz), 9.02 (2H, br), 9.84 (1H, t, *J* = 6.0 Hz); HPLC-MS (ESI): Calcd for C₂₂H₂₆N₄O₄S [M + H]⁺ 443, Found: 443.

Molecular weight: 479.001

Activity grade Ca²⁺:A**Example 22-2**

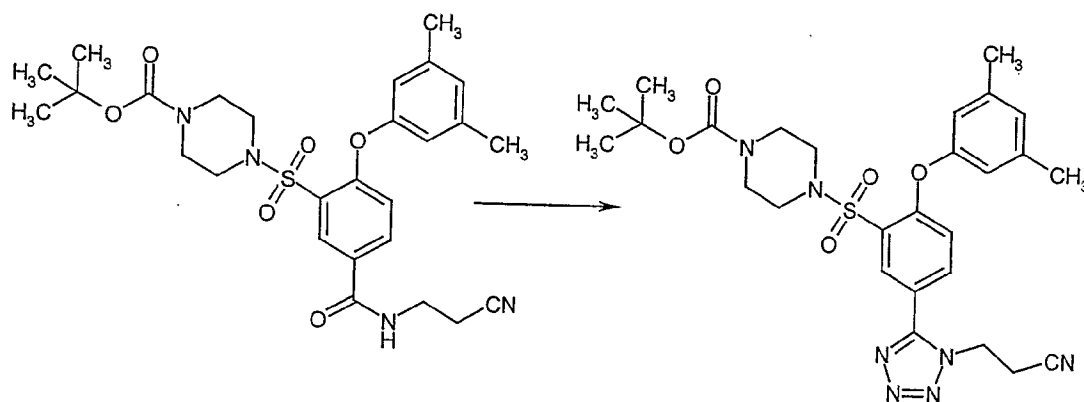
- (1) A mixture of tert-butyl 4-{[5-{[(2-cyanoethyl)amino]carbonyl}-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (0.040 g, 0.074 mmol) and 4 N HCl in 1,4-dioxane (3.0 ml) was stirred for 1.5 hrs. 5N HCl was added, and the stirring was continued for 3 days. The mixture was concentrated in vacuo, and the residue was recrystallized from CH₃CN. The solid obtained was

washed twice with CH₃CN and dried in vacuo to give N-[4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzoyl]-beta-alanineamide hydrochloride (0.036 g, 98.3%): mp 121°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.30 (6H, s), 2.36 (2H, t, *J* = 7.3 Hz), 3.16 (4H, br), 3.42 - 3.46 (6H, m), 6.81 (2H, s), 6.83 (1H, s), 6.94 (1H, s), 6.98 (1H, d, *J* = 8.5 Hz), 7.36 (1H, s), 8.08 (1H, dd, *J* = 2.2, 8.8 Hz), 8.35 (1H, d, *J* = 2.2 Hz), 8.76 (1H, t, *J* = 5.7 Hz), 9.13 (2H, br): HPLC-MS (ESI): Calcd for C₂₂H₂₈N₄O₅S [M + H]⁺ 461, Found: 461.

Molecular weight: 497.017

Activity grade Ca²⁺: A

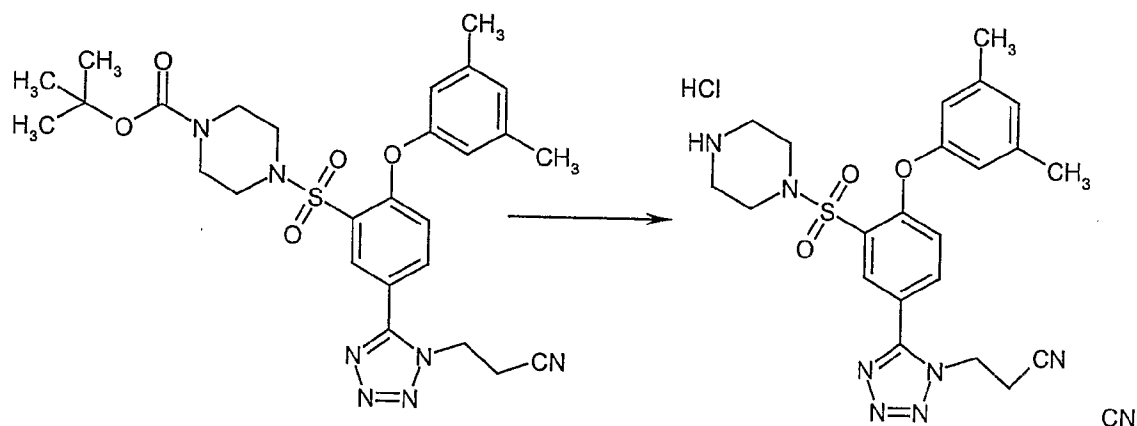
Example 22-3



- (1) To a solution of tert-butyl 4-([5-((2-cyanoethyl)amino)carbonyl]-2-(3,5-dimethylphenoxy)phenyl)sulfonyl-1-piperazinecarboxylate (0.396 g, 0.730 mmol) in CH₃CN (3.0 ml) was added triphenylphosphine (0.230 g, 0.876 g). The mixture was gently heated with a heat gun until a clear solution resulted. The mixture was cooled with an ice-water bath, and diethyl azodicarboxylate (0.138 ml, 0.876 mmol) and azidotrimethylsilane (0.116 ml, 0.876 mmol) were added successively. The mixture was allowed to warm to room temperature, and the stirring was continued overnight. A solution of triphenylphosphine (0.115 g, 0.438 mmol), diethyl azodicarboxylate (0.069 ml, 0.438 mmol) and azido-trimethylsilane (0.058 ml, 0.437 mmol) were added successively, and the

- 169 -

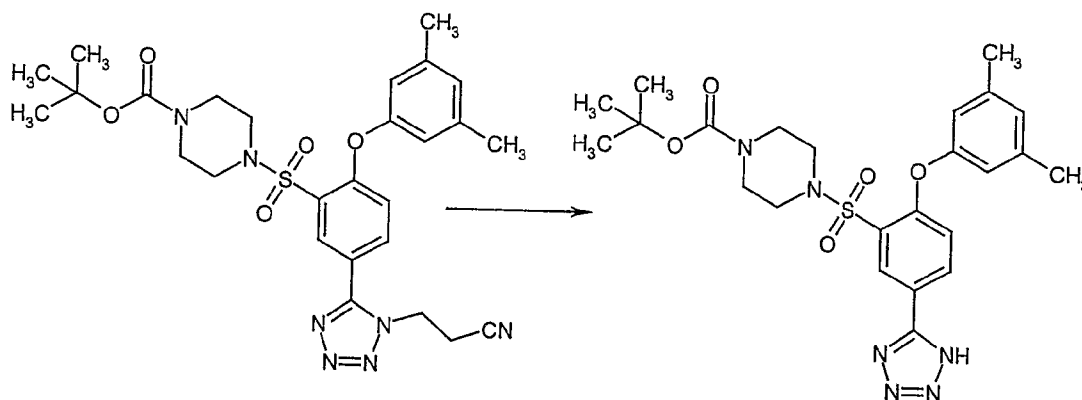
5 mixture was stirred for 3 days. The mixture was diluted with EtOAc, and washed with water. The separated organic phase was washed with saturated NaHCO₃ solution, water and brine, dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (Hexane/EtOAc=1/1) to give tert-butyl 4-{{[5-[1-(2-cyanoethyl)-1H-tetraazol-5-yl]-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarb-



- 10 (2) To a solution of tert-butyl 4-{{[5-[1-(2-cyanoethyl)-1H-tetraazol-5-yl]-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-1-piperazinecarboxylate (0.030 g, 0.053 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture was stirred at room temperature for 2 hrs, then concentrated in vacuo. The residue was recrystallized from Et₂O, washed with Et₂O and dried in vacuo to give
- 15 3-{{[5-[4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)phenyl]-1H-tetrazol-1-yl]propanenitrile hydrochloride (0.021 g, 78.8%):mp 125°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.32 (6H, s), 3.18 (4H, br), 3.23 (2H, t, *J* = 6.3 Hz), 3.50 (4H, br), 4.76 (2H, t, *J* = 6.3 Hz), 6.89 (2H, s), 6.99 (1H, s), 7.10 (1H, d, *J* = 8.5 Hz), 8.04 (1H, dd, *J* = 1.9, 8.5 Hz), 8.26 (1H, d, *J* = 1.9 Hz), 9.05 (2H, br); HPLC-MS (ESI): Calcd for C₂₂H₂₅N₇O₃S [M + H]⁺ 468, Found: 468.
- 20

Molecular weight:504.014

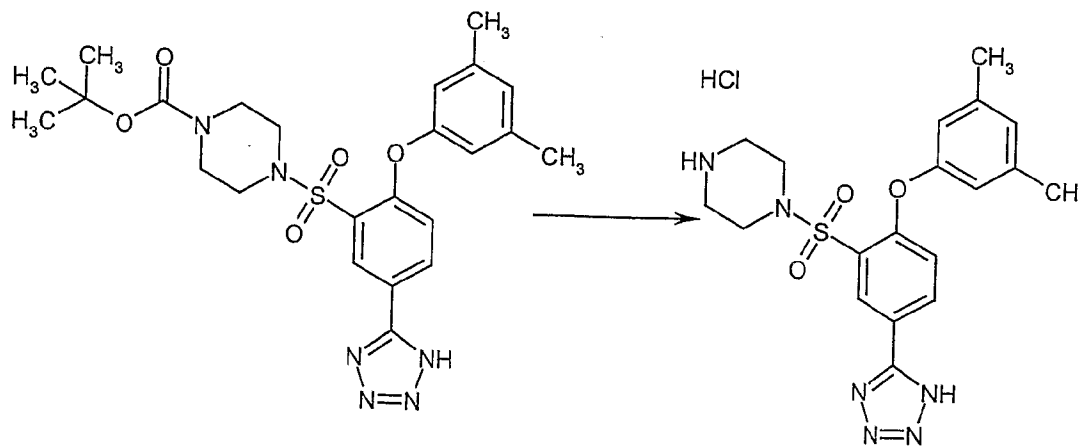
Activity grade Ca²⁺: A

Example 22-4

5

- (1) To a solution of tert-butyl 4-([5-[1-(2-cyanoethyl)-1H-tetrazol-5-yl]-2-(3,5-dimethylphenoxy)phenyl]sulfonyl)-1-piperazinecarboxylate (0.150 g, 0.264 mmol) in CH_2Cl_2 (2.0 ml) was added DBU (0.119 ml, 0.793 mmol), and the mixture was stirred at room temperature for 2.5 hrs. The mixture was diluted with EtOAc, and washed with 1N HCl. The separated organic phase was washed with water and brine, dried over Na_2SO_4 . The solvent was evaporated in vacuo. The residue was recrystallized from Et_2O . The solid was collected by filtration, washed with Et_2O and dried in vacuo to give tert-butyl 4-([2-(3,5-dimethylphenoxy)-5-(1H-tetrazol-5-yl)phenyl]sulfonyl)-1-piperazinecarboxylate (0.096 g, 70.6%).

15

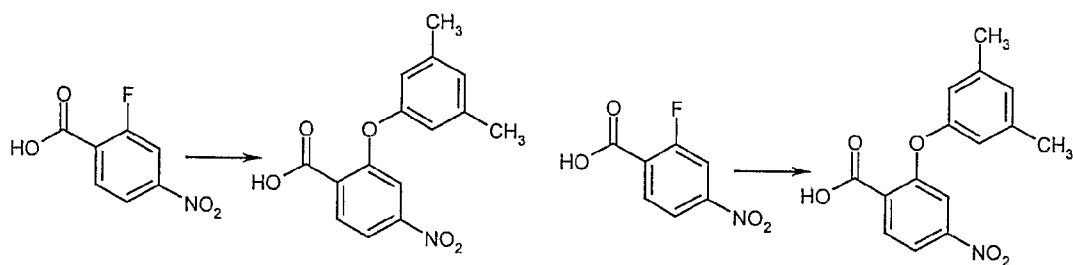


- (2) To a solution of tert-butyl 4-{{[2-(3,5-dimethylphenoxy)-5-(1H-tetraazol-5-yl)phenyl]sulfonyl}-1-piperazinecarboxylate (0.050 g, 0.097 mmol) in 1,4-dioxane (1.0 ml) was added 4N HCl in 1,4-dioxane (3.0 ml). The mixture was stirred at room temperature for 2 hrs. The precipitate was collected by filtration, washed with 1,4-dioxane and Et₂O, dried in vacuo to give 1-{{[2-(3,5-dimethylphenoxy)-5-(1H-tetraazol-5-yl)phenyl]sulfonyl}piperazine hydrochloride (0.037 g, 84.4%): mp 213°C ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.31 (6H, s), 3.18 (4H, br), 3.48 (4H, br), 6.86 (2H, s), 6.96 (1H, s), 7.14 (1H, d, *J* = 8.8 Hz), 8.29 (1H, dd, *J* = 2.2, 8.8 Hz), 8.56 (1H, d, *J* = 2.2 Hz), 9.07 (2H, br); HPLC-MS (ESI): Calcd for C₁₉H₂₂N₆O₃S [M + H]⁺ 415, Found: 415.

Molecular weight: 450.950

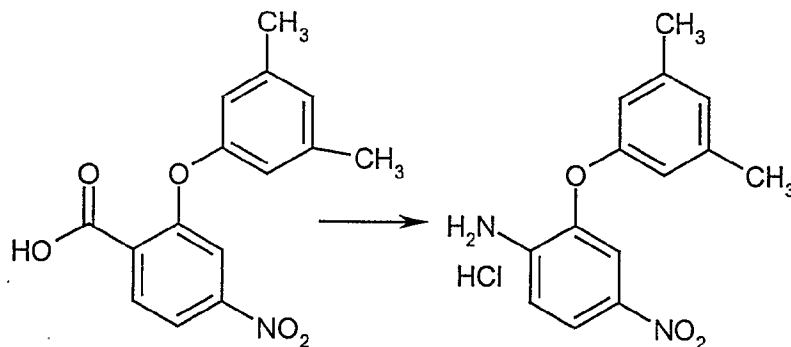
Activity grade Ca²⁺: A

Example 23-1

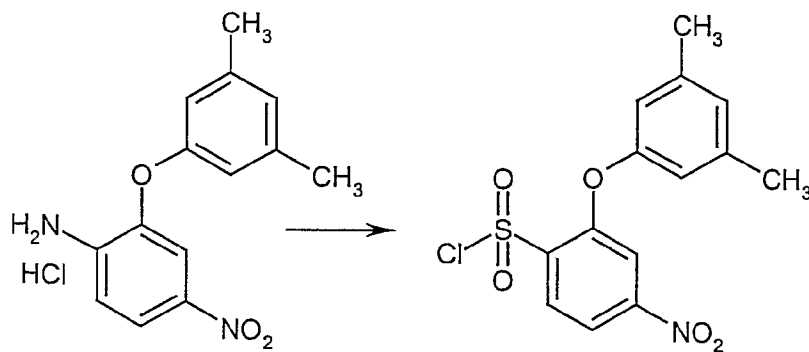


- (1) 2-(3,5-dimethylphenoxy)-4-nitrobenzoic acid was prepared by the same procedure of 4-(3,5-dichlorophenoxy)-3-nitrobenzoic acid (Example 13-(1)).

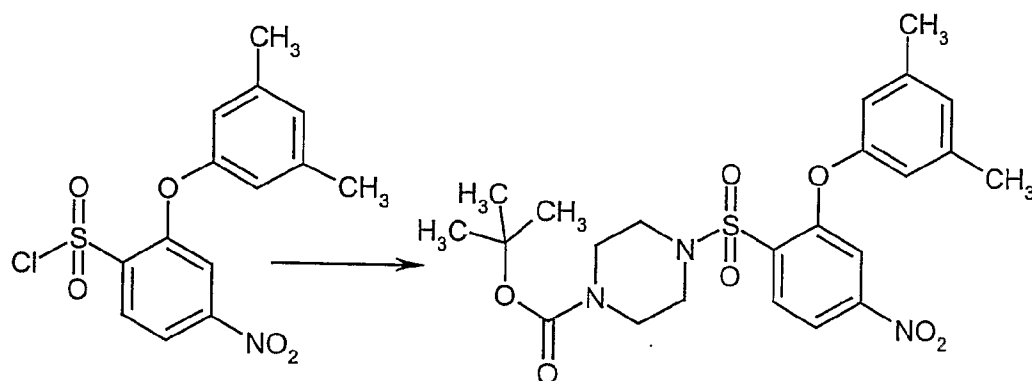
- 172 -



- (2) The mixture of 2-(3,5-dimethylphenoxy)-4-nitrobenzoic acid (1.72 g, 6.00 mmol), diphenyl phosphoroazidate (1.98 g, 7.20 mmol) and triethylamine (1.00 ml, 7.20 mmol) in tert-butanol was heated to 80°C overnight. After cooled to room temperature, the reaction mixture was poured into water and the resulting mixture was extracted with EtOAc. The extract was washed with brine, and dried over MgSO₄. The solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (CHCl₃/Hexane = 65/35) to give a colorless oil. The obtained oil was dissolve into 4N HCl in 1,4-dioxane and the resulting mixture was stirred overnight. Then the reaction mixture was condensed under reduced pressure. The obtained material was dissolved in THF followed addition of ether. The precipitate was collected by filtration, washed with ether and dried in vacuo to give 2-(3,5-dimethylphenoxy)-4-nitroaniline hydrochloride as yellow powder. (0.18 g, 10%)



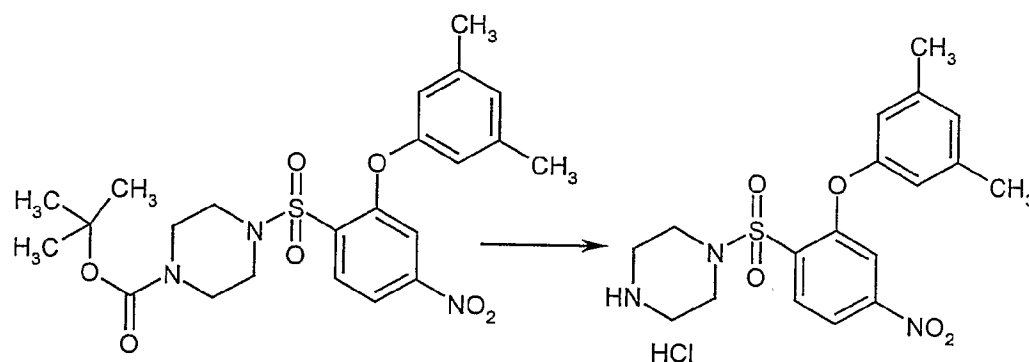
- (3) 2-(3,5-dimethylphenoxy)-4-nitrobenzenesulfonylchloride was prepared by the same procedure of 5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonylchloride (Example 13-(5)).



5

- (4) tert-Butyl 4-{2-(3,5-dimethylphenoxy)-4-nitrophenylsulfonyl}-1-piperazine-carboxylate was prepared by the same procedure of 1-{5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl}-(3S)-(tert-butoxycarbonylamino)pyrrolidine (Example 13-1(6)).

10



- (5) 1-{2-(3,5-dimethylphenoxy)-4-nitrophenylsulfonyl}piperazine hydrochloride was prepared by the same procedure of 1-{5-cyano-2-(3,5-dichlorophenoxy)phenylsulfonyl}-(3S)-aminopyrrolidine hydrochloride (Example 13-(7)):mp 284°C

15

^1H NMR (500 MHz, DMSO- d_6) \square ; 2.32 (6H, s), 3.18-3.19 (4H, m), 3.51-3.53 (4H, m), 6.92 (2H, s), 7.01 (1H, s), 7.52 (1H, d, $J = 1.9$ Hz), 8.08 (1H, dd, $J =$

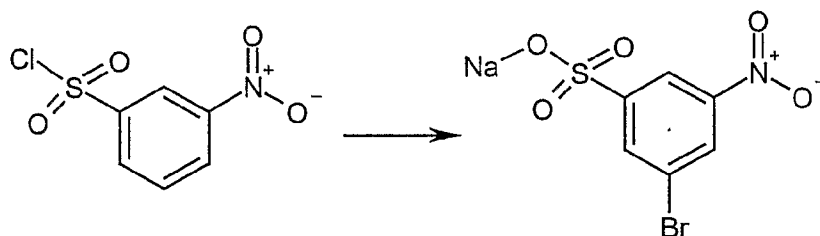
- 174 -

8.5, 2.2 Hz), 8.15 (1H, d, $J = 8.5$ Hz), 9.28 (2H, br); HPLC-MS (ESI): calcd for $C_{18}H_{22}ClFN_2O_3S$ $[M+H]^+$ 392, Found: 392.

Molecular weight: 427.910

5 Activity grade Ca^{2+} :A

Example 24-1

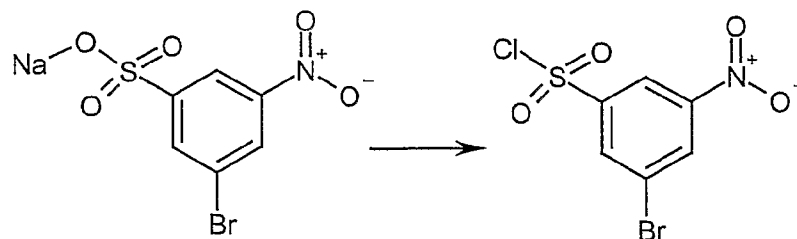


10

- (1) To a vigorously stirred mixture of *m*-nitrobenzenesulfonyl chloride (3.00 g, 13.5 mmol), trifluoroacetic acid (6.5 ml, 84.4 mmol) and conc. sulfuric acid (2.6 ml, 47.8 mmol) was added *N*-bromosuccinimide (3.61 g, 20.3 mmol) in portions over an hour period. This mixture was stirred at 45°C for 88 hrs. The mixture was poured into 25 ml of ice-water, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 to remove very small amount of 3-bromo-5-nitrobenzenesulfonyl chloride. The aqueous layer was concentrated to give a mixture of 3-bromo-5-nitrobenzenesulfonic acid, 3-nitrobenzenesulfonic acid and sulfuric acid. To the mixture was added 8N NaOH and the resulting precipitate was collected by filtration and washed with water to give sodium 3-bromo-5-nitrobenzenesulfonate (256 mg, 6.2%).

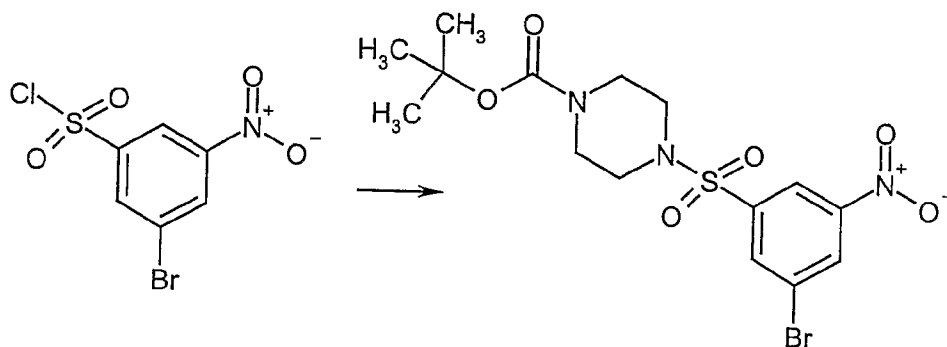
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20



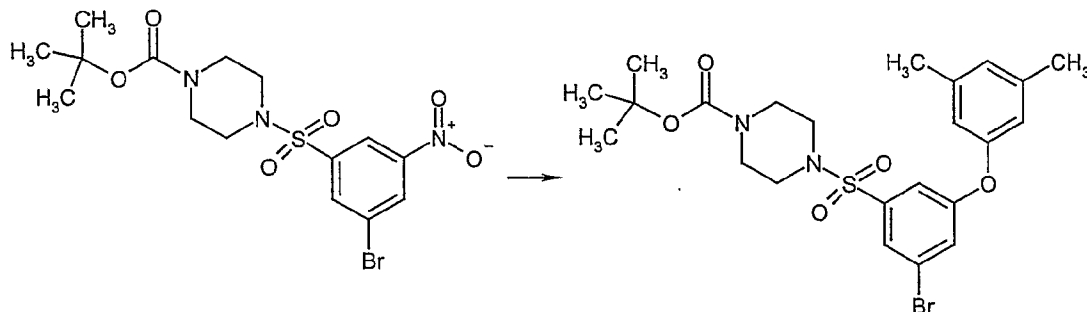
- 175 -

- (2) A suspension of sodium 3-bromo-5-nitrobenzenesulfonate (140 mg, 0.46 mmol) in phosphorus oxychloride (1.0 ml, 10.7 mmol) was refluxed for 1 hr. Phosphorus pentachloride (192 mg, 0.92 mmol) was added and the mixture was stirred at 150°C for additional 1 hr. After cooling to room temperature, the mixture was evaporated. The resulting residue was neutralized with 4N NaOH and the product was extracted with EtOAc. The organic layer was dried over anhydrous MgSO₄. The solvent was evaporated in vacuo to give 3-bromo-5-nitrobenzenesulfonyl chloride (103 mg, 74%).

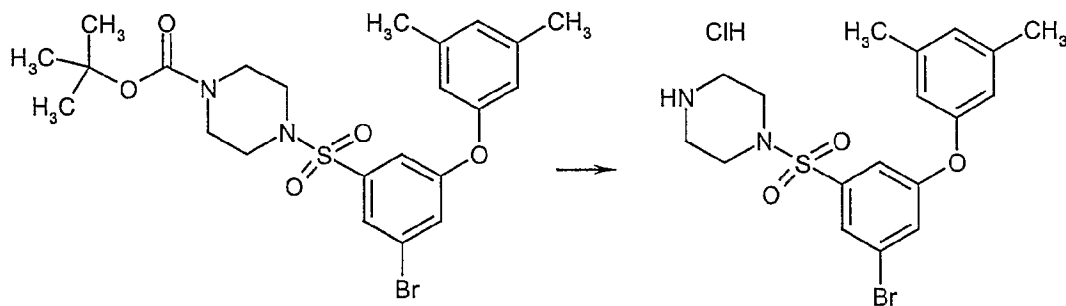


- (3) To a mixture of 3-bromo-5-nitrobenzenesulfonyl chloride (100 mg, 0.33 mmol) and *N,N*-diisopropylethylamine (0.069 ml, 0.40 mmol) in THF (3 ml) was added dropwise the solution of *tert*-butyl 1-piperazinecarboxylate (68 mg, 0.37 mmol) in THF (2 ml) at 0°C. The mixture was stirred at room temperature for 1 hr. Solvent was removed by evaporation. The resulting residue was diluted with CH₂Cl₂ and washed with 0.5 N HCl, brine, aqueous NaHCO₃, and brine, then dried over anhydrous MgSO₄. The solvent was removed by evaporation and the residue was purified by preparative TLC on silica gel (Hexane/EtOAc=2/1) to give *tert*-butyl 4-[(3-bromo-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (116 mg, 77%); MS (FAB): Calcd for C₁₅H₂₀BrN₃O₆S [M+H]⁺ 450 and 452, Found: 350 and 352 (-Boc).

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- (4) To a suspension of sodium hydride (6.7 mg, 0.17 mmol) in DMF (2 ml) was added 3,5-dimethylphenol (20 mg, 0.17 mmol) at 0°C. This mixture was stirred for 10 min. *tert*-butyl 4-[(3-bromo-5-nitrophenyl)sulfonyl]-1-piperazinecarboxylate (50 mg, 0.11 mmol) was added to and the mixture was stirred at 90°C for 2.5 hrs. The reaction mixture was diluted with EtOAc and washed with aqueous NaHCO₃ and brine. The organic layer was dried over anhydrous MgSO₄. The solvent was evaporated in vacuo. The residue was purified by preparative TLC on silica gel (Hexane/EtOAc=2/1). The resulting solid was suspended in ether/hexane/CHCl₃ and collected by filtration to give *tert*-butyl 4-[[3-bromo-5-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (19.5 mg, 33%); mp 155 °C; HPLC-MS (ESI): Calcd for C₂₃H₂₉BrN₂O₅S [M+H]⁺ 525 and 527, Found: 425 and 427 (-Boc).



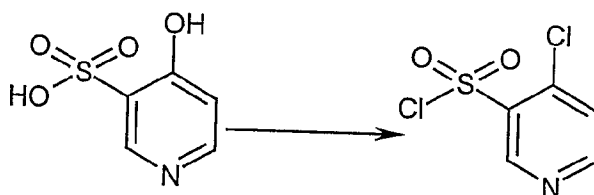
- (5) A solution of *tert*-butyl 4-[[3-bromo-5-(3,5-dimethylphenoxy)phenyl]sulfonyl]-1-piperazinecarboxylate (17 mg, 0.032 mmol) in 4N HCl solution in 1,4-dioxane (2 ml, 8 mmol) was stirred at room temperature overnight. Solvent was removed by evaporation to give 1-[[3-bromo-5-(3,5-dimethyl-

phenoxy)phenyl]sulfonyl}piperazine hydrochloride (14.9 mg, 99%): mp
 >84°C (decomposed); ¹H NMR (500 MHz, DMSO-d₆) δ 2.30 (6H, s), 3.20
 (8H, br), 6.79 (2H, s), 6.93 (1H, s), 7.25 (1H, s), 7.60 (1H, d, J=2.0 Hz), 7.66
 (1H, s), 8.99 (1H, br); HPLC-MS (ESI): Calcd for C₁₈H₂₁BrN₂O₃S [M+H]⁺
 425 and 427, Found: 425 and 427.

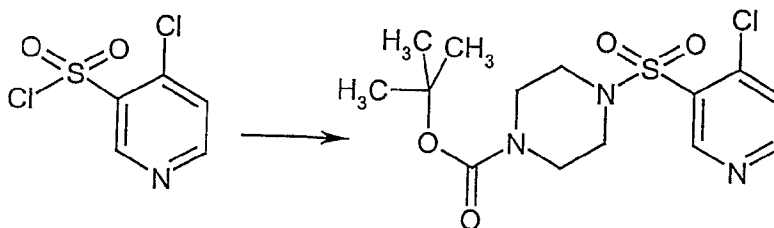
Molecular weight: 461.808

Activity grade Ca²⁺:A

10 Example 25-1

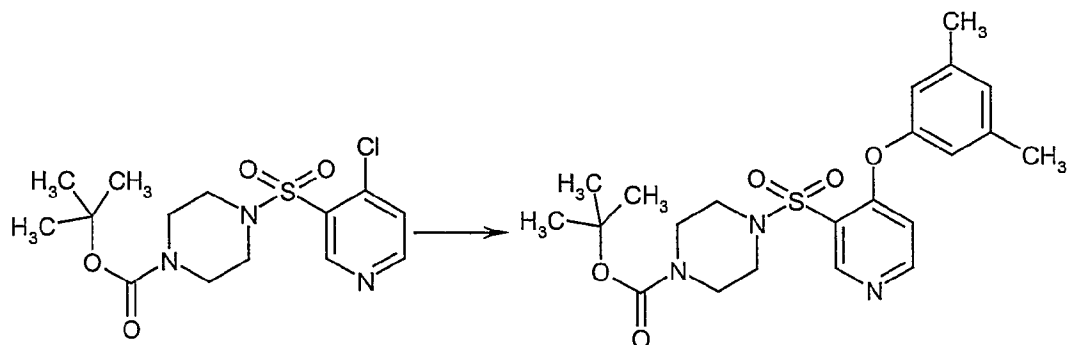


- (1) To a mixture of 4-hydroxypyridine-3-sulfonic acid (1.00 g, 5.71 mmol) and
 phosphorus pentachloride (2.38 g, 11.4 mmol) was added phosphorus oxy-
 chloride (1.06 ml, 11.4 mmol) dropwise at 0°C. The mixture was refluxed for
 5 hrs. After the mixture was cooled to room temperature, cooled aqueous
 NaHCO₃ was added to the mixture carefully. The mixture was extracted with
 CHCl₃. The organic layer was dried over anhydrous MgSO₄. The solvent was
 evaporated in vacuo to give 4-chloro-3-pyridinesulfonyl chloride as colorless
 oil (0.97 g, 80.1 %).



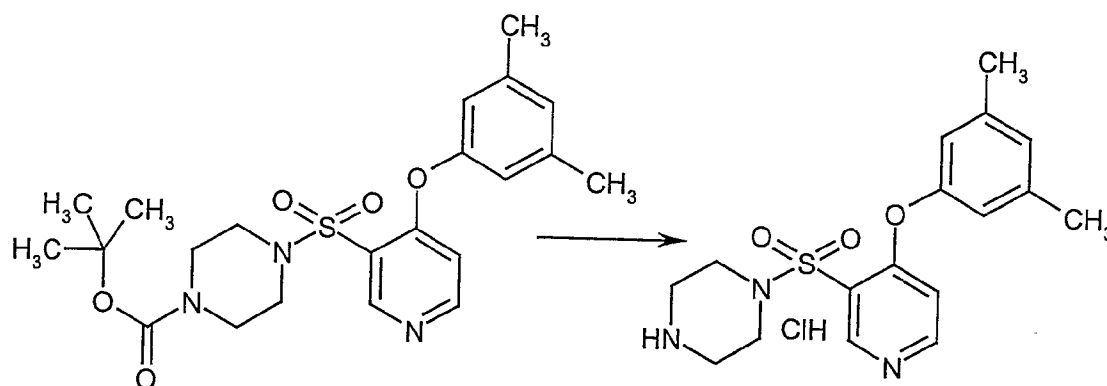
- 178 -

- (2) A mixture of 4-chloro-3-pyridinesulfonyl chloride (0.97 g, 4.57 mmol), *tert*-butyl 1-piperazinecarboxylate (0.94 g, 5.03 mmol), and *N,N*-diisopropylethylamine (0.88 ml, 5.03 mmol) in THF (50 ml) was stirred at room temperature overnight. The mixture was concentrated *in vacuo*. The residue was washed with ice water, then was dried *in vacuo* to give *tert*-butyl 4-[(4-chloro-3-pyridinyl)sulfonyl]-1-piperazinecarboxylate as a pale yellow solid (1.51 g, 91.3 %).



- (3) To a solution of 3,5-dimethylphenol (37.1 mg, 0.30 mmol) in 1,4-dioxane (1ml) was added sodium hydride (60 % oil suspension, 13.3 mg, 0.33 mmol) portionwise. The mixture was stirred at room temperature for 30 min. To the mixture was added a solution of *tert*-butyl 4-[(4-chloro-3-pyridinyl)sulfonyl]-1-piperazinecarboxylate (100 mg, 0.28mmol) in 1,4-dioxane (1ml) slowly. The mixture was stirred at 70°C overnight. After the mixture was cooled to room temperature, the mixture was concentrated *in vacuo*. The residue was washed with ice water, dried *in vacuo* to give *tert*-butyl 4-[[4-(3,5-dimethylphenoxy)-3-pyridinyl]sulfonyl]-1-piperazinecarboxylate (110 mg, 88.9 %) as a white solid.

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- (4) To a solution of *tert*-butyl 4-{[4-(3,5-dimethylphenoxy)-3-pyridinyl]sulfonyl}-1-piperazinecarboxylate (23.4 mg, 0.0523 mmol) in CH₂Cl₂ (1ml) was added 4N HCl in 1,4-dioxane (0.25 ml). The mixture was stirred at room temperature overnight. The mixture was concentrated *in vacuo*. The residue was triturated with diethylether, dried *in vacuo* to give 1-{[4-(3,5-dimethylphenoxy)-3-pyridinyl]sulfonyl}piperazine hydrochloride (17 mg, 76 %) as a white solid: mp 220°C; ¹H NMR (300 MHz, DMSO-d₆) δ 2.33 (6H, s), 3.19 (4H, m), 3.52 (4H, m), 6.84 (1H, d, J = 6 Hz), 7.00 (2H, s), 7.03 (1H, s), 8.65 (1H, d, J = 6 Hz), 8.88 (1H, s), 9.35 (2H, br); HPLC-MS (ESI): Calcd for C₁₇H₂₁N₃O₃S [M+H]⁺ 348, Found: 348.

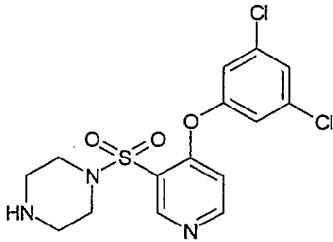
Molecular weight: 420.361

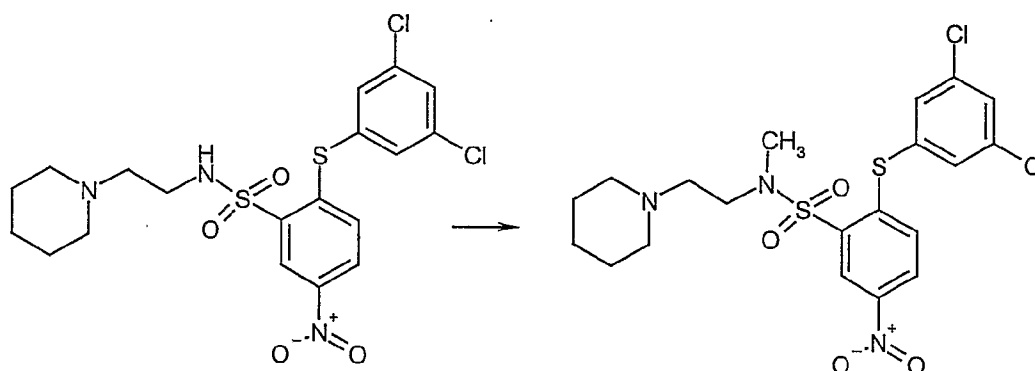
Activity grade RBA: B

Activity grade Ca²⁺: A

In the similar manner as described in Example 25-1 above, compounds in Example 25-2 as shown in Table 25 were synthesized.

Table 25

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
25-2	 ClH	461.19704	388	213-215	A	A

Example 26-1

- (1) To a suspension of sodium hydride (4.5 mg, 0.11 mmol) in THF (2 ml) was added
 5 2-[(3,5-dichlorophenyl)sulfanyl]-5-nitro-*N*-[2-(1-piperidinyl)ethyl]benzenesulfon-
 amide (50 mg, 0.10 mmol) at 0°C. The mixture was stirred at 0°C for 10 min.
 Methyl iodide (0.01 ml, 0.15 mmol) was added and the mixture was stirred at
 0°C for 30 min then room temperature overnight. The reaction mixture was
 diluted with EtOAc and washed with aqueous NaHCO₃ and brine. The organic
 10 layer was dried over anhydrous MgSO₄. The solvent was evaporated in vacuo.
 The residue was purified by preparative TLC on silica gel (CHCl₃/MeOH=9/1)
 to give 2-[(3,5-dichlorophenyl)sulfanyl]-*N*-methyl-5-nitro-*N*-[2-(1-piperidinyl)-
 ethyl]benzenesulfonamide (18 mg, 35.0%): mp 113-114 °C; ¹H NMR (300
 MHz, CDCl₃) δ 1.42 (2H, m), 1.52 (4H, m), 2.41 (4H, m), 2.57 (2H, t, *J*=7.0
 15 Hz), 3.03 (3H, s), 3.47 (2H, t, *J*=7.0 Hz), 7.07 (1H, d, *J*=8.7 Hz), 7.45 (2H,
 m), 7.51 (1H, t, *J*=1.9 Hz), 8.14 (1H, dd, *J*=2.3, 8.7 Hz), 8.79 (1H, d, *J*=2.3
 Hz); HPLC-MS (ESI): Calcd for C₂₀H₂₃Cl₂N₃O₄S₂ [M+H]⁺ 504 and 506,
 Found: 504 and 506.

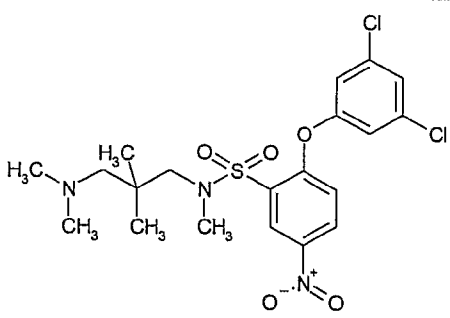
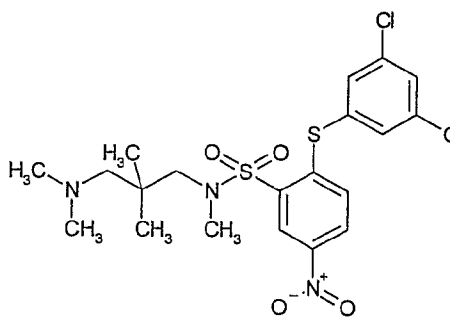
20 Molecular weight: 504.458

Activity grade RBA: A

Activity grade Ca²⁺: A

25 In the similar manner as described in Example 26-1 above, compounds in Example
 26-2 and 26-3 as shown in Table 26 were synthesized.

Table 26

EX.No.	molstructure	MW	M+1	mp	RBA	Ca2+
26-2		490.40935	490	108-110		A
26-3		506.47395	506	144-145		A

Operative examples relating to pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

5

Tablet**Composition**

10 100 mg of the compound of Example 1-1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, curvature radius 12 mm.

15

Preparation

The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (tablet format, see above). The moulding force applied is typically 15 kN.

20

Orally administrable suspension**Composition**

25

1000 mg of the compound of Example 1-1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

30 A single dose of 100 mg of the compound according to the invention is provided by 10 ml of oral suspension.

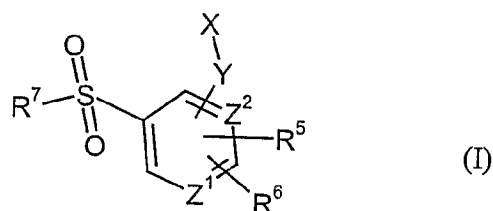
- 184 -

Preparation

5 The Rhodigel is suspended in ethanol and the active component is added to the suspension. The water is added with stirring. Stirring is continued for about 6h until the swelling of the Rhodigel is complete.

CLAIMS

1. A sulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



- 10 X represents phenyl, which is substituted by 0 to 5 substituents independently selected from the group consisting of R^1 , R^2 , R^3 , R^4 and R^0 or pyridine, which is substituted by 0 to 5 substituents independently selected from the group consisting of R^1 , R^2 , R^3 and R^4

wherein

- 15 R^1 is hydrogen, halogen, hydroxy, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxy carbonyl, amino, straight- or branched- C_{1-6} alkylamino, di(straight- or branched- C_{1-6} alkyl)amino, straight- or
20 branched- C_{1-6} alkanoyl, nitro, or phenyl,

- R^2 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, or cyano, or

- 25 R^1 and R^2 together form benzene ring or C_{5-8} cycloalkyl fused to the adjacent phenyl or pyridine,

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R³ is hydrogen, halogen, or straight- or branched- C₁₋₆ alkyl,

R⁴ is hydrogen, halogen, or straight- or branched- C₁₋₆ alkyl,

R⁰ is hydrogen, halogen, or straight- or branched- C₁₋₆ alkyl,

Y represents O, NH, NCH₃, S, S(O), or SO₂;

Z¹ represents CH or N;

Z² represents CH or N

with the proviso that both Z¹ and Z² cannot be N at the same time;

R⁵ represents hydrogen, halogen, hydroxy, straight- or branched -C₁₋₆ alkyl optionally substituted by mono, di or tri halogen or hydroxy, straight- or branched -C₁₋₆ alkoxy, straight- or branched -C₁₋₆ alkoxycarbonyl, amino, straight- or branched- C₁₋₆ alkanoylamino, phenyl-(CH₂)_q -carbonylamino (wherein q represents an integer selected from 0 to 6), straight- or branched- C₁₋₆ alkylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, carboxy, straight- or branched- C₁₋₆ alkyl sulfonyl, oxazolidinonyl, or substituents represented by the formula, -SO₂-NR⁵¹R⁵², or -CO-NR⁵¹R⁵²,

wherein

R⁵¹ and R⁵² are independently selected from the group consisting of hydrogen, straight- or branched- C₁₋₆ alkyl optionally substituted by cyano or carbamoyl and tetrazolyl optionally substituted by C₁₋₆ alkyl nitrile, or

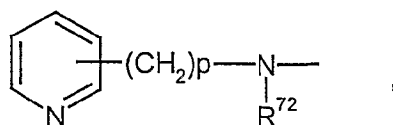
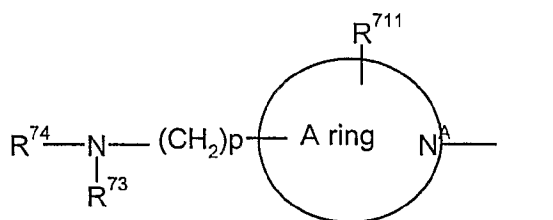
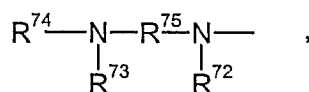
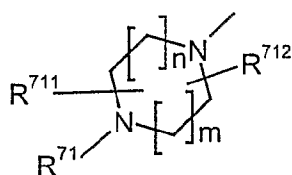
- 187 -

R^{51} and R^{52} may form, together with the adjacent N, a saturated 5 to 8 membered ring optionally interrupted by NH,

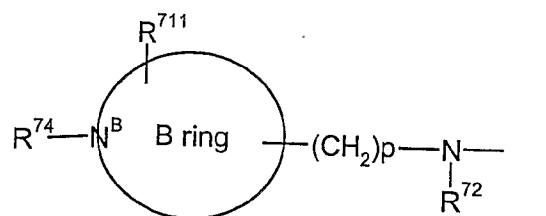
5 R^6 represents hydrogen, halogen, straight or branched C_{1-6} alkyl optionally substituted by mono di or tri halogen, or straight or branched C_{1-6} alkoxy, or

10 R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl, or pyridine; and

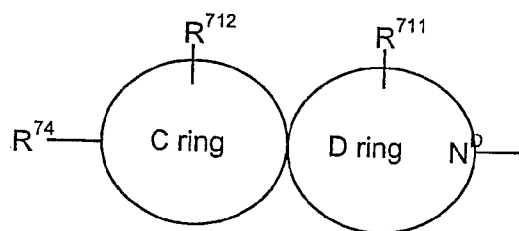
R^7 represents



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or



wherein

n represents an integer selected from 1 to 3,

5

m represents an integer selected from 0 to 3,

10

R^{71} is hydrogen, C_{3-8} cycloalkyl optionally interrupted by NH, N- CH_3 or O, straight- or branched C_{1-6} alkoxy carbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, formyl, or

straight- or branched C_{1-6} alkyl

15

wherein the alkyl is optionally substituted by hydroxy, straight- or branched- C_{1-6} alkoxy, hydroxy straight- or branched- C_{1-6} alkoxy, carboxy, straight- or branched- C_{1-6} alkoxy carbonyl, straight- or branched- C_{1-6} alkylthio, di(straight- or branched- C_{1-6} alkyl)amino, mono, di or tri halogen, or C_{3-8} cycloalkyl optionally interrupted by NH or O,

20

5 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carboxy, cyano, straight-or branched C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono, di or tri halogen, carbamoyl, di (straight-or branched C_{1-6} alkyl)amino carbonyl, and $-NR^{711a}R^{711b}$

wherein

10 R^{711a} and R^{711b} are independently selected from the group consisting of hydrogen, straight- or branched- C_{1-6} alkyl, straight- or branched- C_{1-6} alkanoyl, and straight- or branched- C_{1-6} alkylsulfonyl, or

15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;

20 R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,

R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl optionally substituted by phenyl, or

25 R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally substituted by C_{1-6} alkyl and optionally interrupted by NH or O;

30 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

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A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

5 B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

10

2. The sulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

15

R⁵ is chloro, iodo, nitro, or cyano; and

R⁶ is hydrogen.

20 3. The sulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

25 R¹ is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

R² is halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

30

R³ is hydrogen;

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R^4 is hydrogen;

R^0 is hydrogen;

5

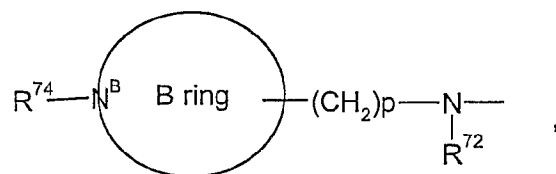
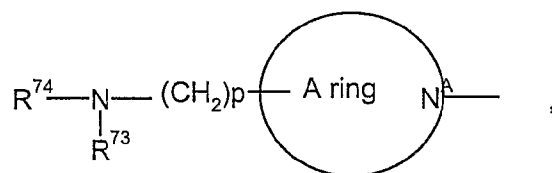
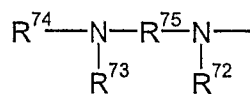
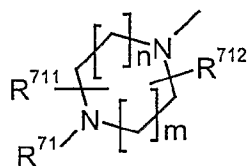
Y is O, NH, NCH₃, S, S(O), or SO₂;

R^5 is halogen, nitro, or cyano;

10

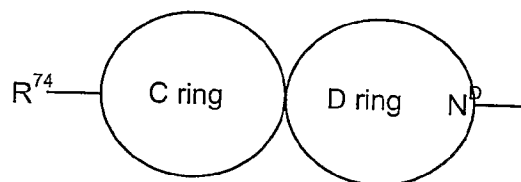
R^6 is hydrogen; and

R^7 represents



- 192 -

or



wherein

n represents an integer selected from 1 to 3,

5

m represents an integer selected from 0 to 3,

10

R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxy carbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

15

R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, carboxy, and straight- or branched C_{1-6} alkyl, or

20

R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl,

R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,

25

R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or

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R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

5 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

10 A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

15 C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

4. The sulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

20

wherein

R^1 and R^2 are identical or different and represent chloro, or methyl;

25 R^3 is hydrogen or fluoro;

R^4 is hydrogen;

30 R^0 is hydrogen;

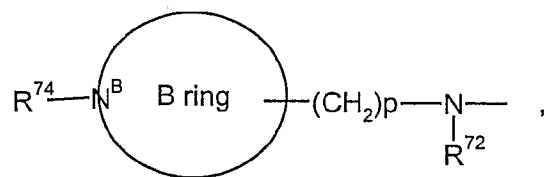
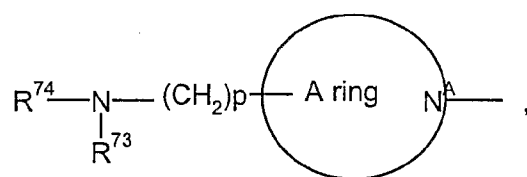
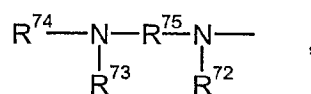
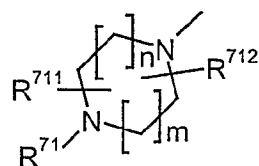
Y is O, NH, NCH_3 , S, $S(O)$, or SO_2 ;

- 194 -

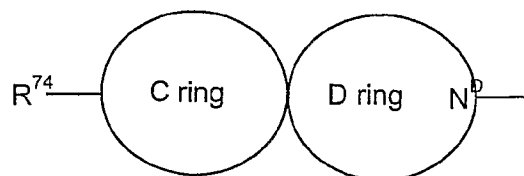
R^5 is chloro, iodo, nitro, or cyano;

R^6 is hydrogen; and

5 R^7 represents



or



wherein

n represents an integer selected from 1 to 3,

- 195 -

- m represents an integer selected from 0 to 3,
- 5 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,
- 10 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, carboxy, and straight-or branched C_{1-6} alkyl, or
- 15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;
- R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;
- R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,
- 20 R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or
- R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;
- 25 R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;
- p represents an integer selected from 0 to 4;
- 30

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A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

5 B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

10 5. The sulfonamide derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

15 R¹ is hydrogen, fluoro, chloro, bromo, methyl, isopropyl, butyl, tert-butyl, trifluoromethyl, methoxy, amino, dimethylamino, acetyl, or nitro;

R² is hydrogen, fluoro, chloro, methyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, or cyano;

20

R³ is hydrogen or fluoro;

R⁴ is hydrogen;

25

R⁰ is hydrogen;

Y is O, NH, NCH₃, S, S(O), or SO₂;

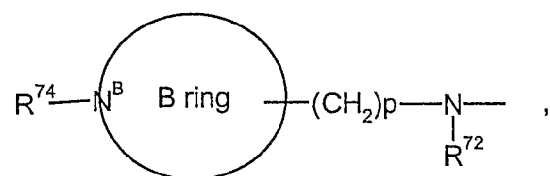
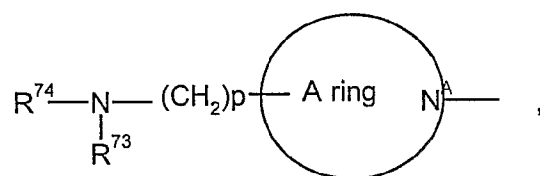
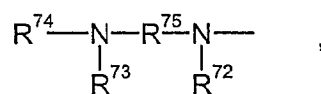
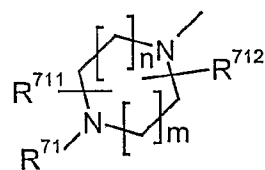
R⁵ is chloro, iodo, nitro, or cyano;

30

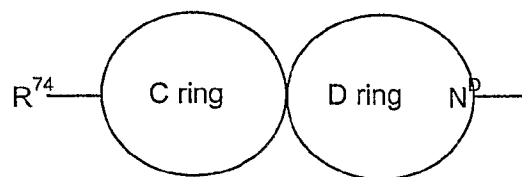
R⁶ is hydrogen; and

- 197 -

R^7 represents



or



wherein

5

n represents an integer 1,

m represents an integer selected from 1 or 2,

- 198 -

R^{71} represents hydrogen, methyl, ethyl or isopropyl;

R^{711} represents hydrogen, methyl, or carboxy;

5 R^{712} represents hydrogen or methyl, or

R^{71} and R^{711} may form, together with the adjacent N atom, a 5 membered saturated ring;

10 R^{72} is hydrogen, methyl, or ethyl;

R^{73} is hydrogen, or methyl,

15 R^{74} is hydrogen, methyl, or ethyl, or

R^{73} and R^{74} may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

20 R^{75} is phenyl;

p represents an integer selected from 0 to 4;

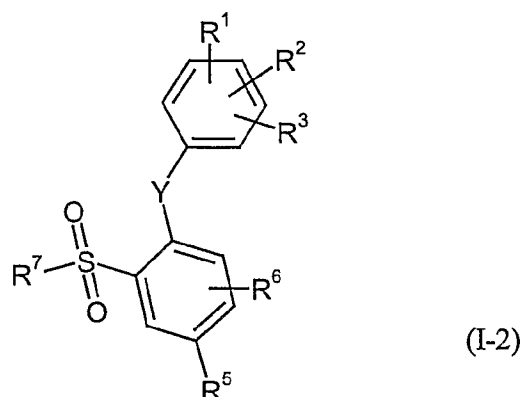
A ring represents piperidino, or pyrrolidino;

25 B ring represents pyrrolidino; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

30 6. The sulfonamide derivative its tautomeric or stereoisomeric form, or a salt thereof according to claim 1 which has the general formula (I-2):

- 199 -



wherein

- 5 R^1 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxy carbonyl, amino, straight- or branched- C_{1-6} alkylamino, di(straight- or branched- C_{1-6} alkyl)amino, straight- or branched- C_{1-6} alkanoyl, or nitro,
- 10 R^2 is hydrogen, halogen, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen, straight- or branched- C_{1-6} alkoxy, or cyano, or
- 15 R^1 and R^2 may form benzene ring or C_{5-8} cycloalkyl fused to the adjacent phenyl;
- R^3 is hydrogen or halogen,
- 20 Y represents O, NH, NCH_3 , S, $S(O)$, or SO_2 ;
- R^5 is hydrogen, halogen, hydroxy, straight- or branched- C_{1-6} alkyl optionally substituted by mono, di, or tri halogen or hydroxy, straight- or branched- C_{1-6} alkoxy, straight- or branched- C_{1-6} alkoxycarbonyl,

- 200 -

amino, straight- or branched- C₁₋₆ alkanoylamino, phenyl-(CH₂)_q-carbonylamino (wherein q represents an integer selected from 0 to 6), straight- or branched- C₁₋₆ alkylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, carboxy, straight- or branched- C₁₋₆ alkyl sulfonyl, oxazolidinonyl, or substituents represented by the formula, -SO₂-NR⁵¹R⁵², or -CO-NR⁵¹R⁵²,

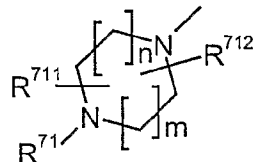
wherein

R⁵¹ and R⁵² are independently selected from the group consisting of hydrogen, straight- or branched- C₁₋₆ alkyl optionally substituted by cyano or carbamoyl, tetrazolyl optionally substituted by C₁₋₆ alkyl nitrile, or R⁵¹ and R⁵² may form, together with the adjacent N, a saturated 5 to 8 membered ring optionally interrupted by NH,

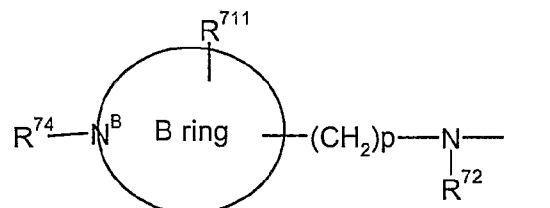
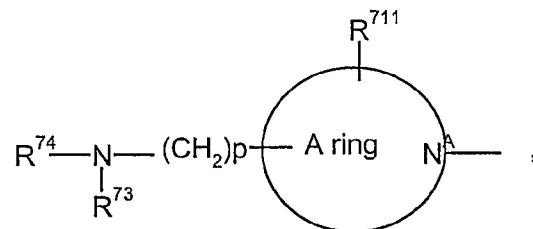
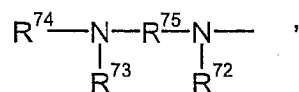
R⁶ is hydrogen, halogen, straight or branched C₁₋₆ alkyl optionally substituted by mono, di or tri halogen, or straight or branched C₁₋₆ alkoxy, or

R⁵ and R⁶ may form a pyrrol ring fused to adjacent phenyl; and

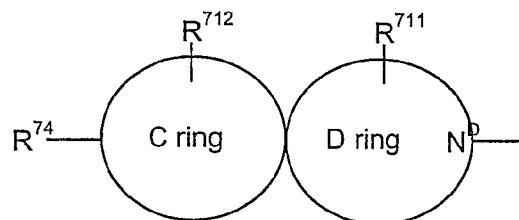
R⁷ represents



- 201 -



or



wherein

n represents an integer selected from 1 to 3,

5

m represents an integer selected from 0 to 3,

10

R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

- 202 -

5 R^{711} and R^{712} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carboxy, cyano, straight-or branched C_{1-6} alkyl optionally substituted by hydroxy, carboxy, or mono, di or tri halogen, carbamoyl, di (straight-or branched C_{1-6} alkyl)amino carbonyl, or $-NR^{711a}R^{711b}$

wherein

10 R^{711a} and R^{711b} are independently selected from the group consisting of hydrogen, straight- or branched- C_{1-6} alkyl, straight- or branched- C_{1-6} alkanoyl, or straight- or branched- C_{1-6} alkylsulfonyl, or

15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;

20 R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,

R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or

25 R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;

30 p represents an integer selected from 0 to 4;

- 203 -

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

5 B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diaza-bicyclic ring.

10 7. The sulfonamide derivative of the formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

wherein

15 R⁵ is chloro, iodo, nitro, or cyano; and

R⁶ is hydrogen.

20 8. The sulfonamide derivative of the formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

wherein

25 R¹ is hydrogen, halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

R² is hydrogen, halogen, or straight- or branched- C₁₋₆ alkyl optionally substituted by mono, di or tri halogen;

30 R³ is hydrogen or halogen,

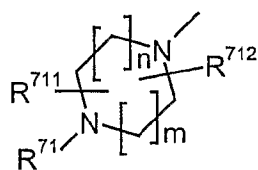
- 204 -

Y is O, NH, NCH₃, S, S(O), or SO₂;

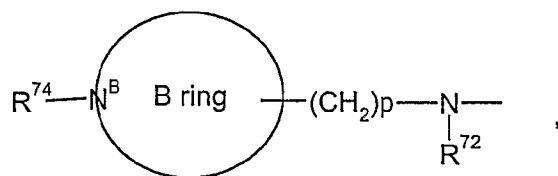
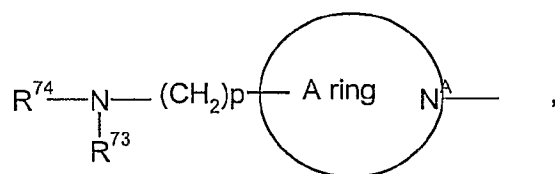
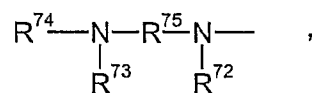
R⁵ is halogen, nitro, or cyano;

5 R⁶ is hydrogen; and

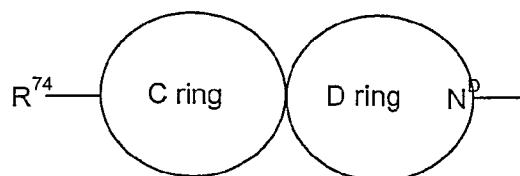
R⁷ represents



10



or



wherein

- 205 -

- n represents an integer selected from 1 to 3,
- m represents an integer selected from 0 to 3,
- 5 R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,
- 10 R^{711} represents hydrogen, methyl, or carboxy,
- R^{712} represents hydrogen or methyl, or
- 15 R^{71} and R^{711} may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;
- R^{72} is hydrogen, or straight- or branched- C_{1-6} alkyl;
- 20 R^{73} is hydrogen, or straight- or branched- C_{1-6} alkyl,
- R^{74} is hydrogen, or straight- or branched- C_{1-6} alkyl, or
- 25 R^{73} and R^{74} may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;
- R^{75} is straight- or branched- C_{1-6} alkylene or a 3 to 8 membered saturated or unsaturated ring;
- 30 p represents an integer selected from 0 to 4;

- 206 -

A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

5 B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

10

9. The sulfonamide derivative of the formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

wherein

15

R¹, R² and R³ are independently selected from the group consisting of hydrogen, chloro, or methyl;

Y is O, NH, NCH₃, S, S(O), or SO₂;

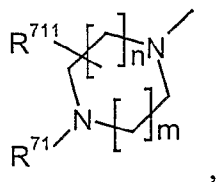
20

R⁵ is chloro, iodo, nitro, or cyano;

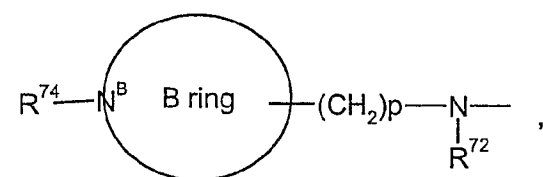
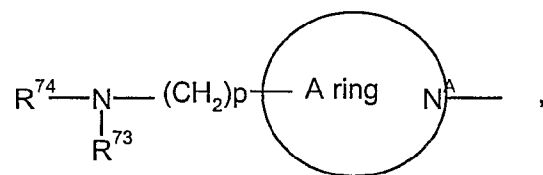
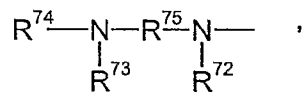
R⁶ is hydrogen; and

25

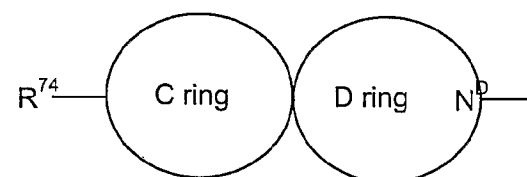
R⁷ represents



- 207 -



or



wherein

5

n represents an integer selected from 1 to 3,

m represents an integer selected from 1 to 3,

10

R^{71} is hydrogen, straight- or branched C_{1-6} alkyl optionally substituted by hydroxy or hydroxy straight- or branched- C_{1-6} alkoxy, C_{3-8} cycloalkyl, straight- or branched C_{1-6} alkoxycarbonyl, phenyl optionally substituted by straight- or branched C_{1-6} alkyl, benzyl, or formyl,

15

R^{711} represents hydrogen, methyl, or carboxy or

- 208 -

R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 to 8 membered saturated ring;

5 R⁷² is hydrogen, or straight- or branched- C₁₋₆ alkyl;

R⁷³ is hydrogen, or straight- or branched- C₁₋₆ alkyl;

10 R⁷⁴ is hydrogen, or straight- or branched- C₁₋₆ alkyl; or

R⁷³ and R⁷⁴ may form, together with adjacent N atom, a 5 to 8 membered saturated ring optionally interrupted by NH or O;

15 R⁷⁵ is straight- or branched- C₁₋₆ alkylene or a 3 to 8 membered saturated or unsaturated ring;

p represents an integer selected from 0 to 4;

20 A ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^A is the only hetero atom;

B ring represents a 3 to 8 membered saturated ring, in which the nitrogen atom N^B is the only hetero atom; and

25 C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

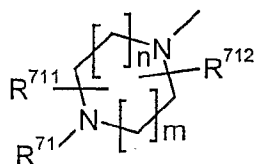
10. The sulfonamide derivative of the formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

30

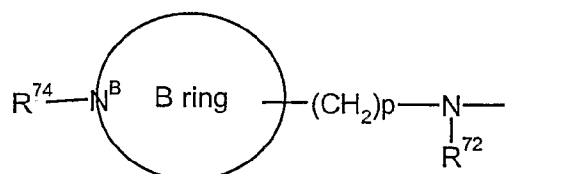
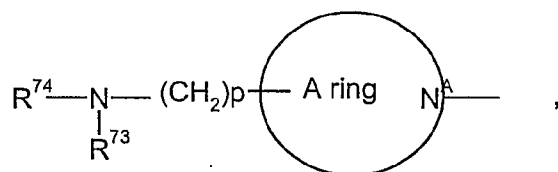
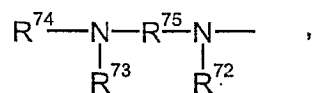
wherein

- 209 -

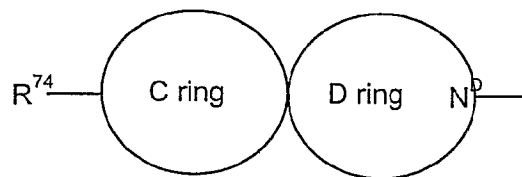
- R^1 is halogen, or straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen;
- 5 R^2 is halogen, or straight- or branched- C_{1-6} alkyl optionally substituted by mono, di or tri halogen;
- R^3 is hydrogen or fluoro;
- 10 Y is O, NH, NCH_3 , S, $S(O)$, or SO_2 ;
- R^5 is hydrogen, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, methoxy, amino, acetamino, isobutylcarbonylamino, tert-butylcarbonylamino, benzoylamino, benzylcarbonylamino, phenethylcarbonylamino, methylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, methylsulfonyl, dimethylaminosulfonyl, piperazinosulfonyl, dimethylaminocarbonyl, or piperazinocarbonyl;
- 15 R^6 is hydrogen, methyl, or methoxy; or
- 20 R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl; and
- R^7 represents



- 210 -



or



wherein

5

n represents an integer 1,

m represents an integer 1 or 2,

10

R^{71} is hydrogen, methyl, ethyl, isopropyl, sec-butyl, branched pentyl, hydroxyethyl, hydroxyethoxyethyl, cyclopentyl, cyclohexyl, tert-butoxycarbonyl, phenyl, tolyl, benzyl, or formyl,

R^{711} represents hydrogen, methyl, or carboxy,

15

R^{712} represents hydrogen or methyl, or

- 211 -

R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 membered saturated ring;

5 R⁷² is hydrogen, methyl, or ethyl;

R⁷³ is hydrogen, or methyl,

10 R⁷⁴ is hydrogen, methyl, or ethyl, or

R⁷³ and R⁷⁴ may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

15 R⁷⁵ is phenyl;

p represents an integer selected from 0 to 4;

A ring represents piperidino, or pyrrolidino;

20 B ring represents pyrrolidino; and

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

25 11. The sulfonamide derivative of formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

wherein

30 R¹ is hydrogen, fluoro, chloro, bromo, methyl, isopropyl, butyl, tert-butyl, trifluoromethyl, methoxy, amino, dimethylamino, acetyl, or nitro;

- 212 -

R^2 is hydrogen, fluoro, chloro, methyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, or cyano;

5 R^3 is hydrogen or fluoro;

Y is O, NH, NCH₃, S, S(O), or SO₂;

10 R^5 is hydrogen, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, methoxy, amino, acetylamino, isobutylcarbonylamino, tert-butylcarbonylamino, benzoylamino, benzylcarbonylamino, phenethylcarbonylamino, methylbenzoylamino, naphthylcarbonylamino, thenoylamino, nitro, cyano, methylsulfonyl, dimethyaminosulfonyl, piperazinosulfonyl, dimethyaminocarbonyl, or piperazinocarbonyl;

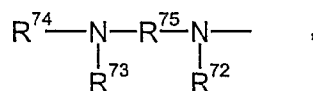
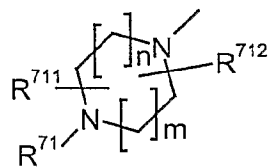
15

R^6 is hydrogen, methyl, or methoxy; or

R^5 and R^6 may form a pyrrol ring fused to adjacent phenyl, and

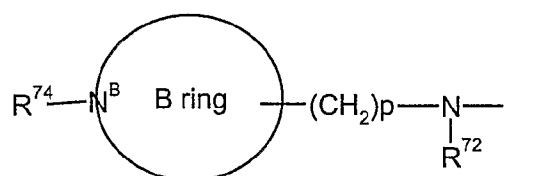
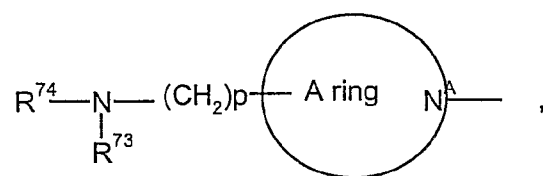
20

R^7 represents

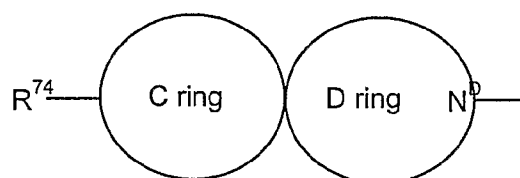


25

- 213 -



or



wherein

5

n represents an integer 1,

m represents an integer 1 or 2,

10

R^{71} represents hydrogen, methyl, ethyl, isopropyl, sec-butyl, branched pentyl, hydroxyethyl, hydroxyethoxyethyl, cyclopentyl, cyclohexyl, tert-butoxycarbonyl, phenyl, tolyl, benzyl, or formyl,

15

R^{711} represents hydrogen, methyl, or carboxy,

R^{712} represents hydrogen or methyl, or

- 214 -

R⁷¹ and R⁷¹¹ may form, together with the adjacent N atom, a 5 membered saturated ring;

5

R⁷² is hydrogen, methyl, or ethyl,

R⁷³ is hydrogen, or methyl,

R⁷⁴ is hydrogen, methyl, or ethyl, or

10

R⁷³ and R⁷⁴ may form, together with adjacent N atom, piperidino, morpholino, or pyrrolidino;

R⁷⁵ is phenyl;

15

p represents an integer selected from 0 to 4;

A ring represents piperidino, or pyrrolidino;

B ring represents pyrrolidino; and

20

C ring and D ring together form a 7 to 12 membered diazabicyclic ring.

12. The sulfonamide derivative of formula (I-2), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 6,

25

wherein

R¹ is chloro, bromo, or methyl;

30

R² is hydrogen, chloro, bromo, or methyl;

- 215 -

R^3 is hydrogen or fluoro;

Y represents O, S, or S(O);

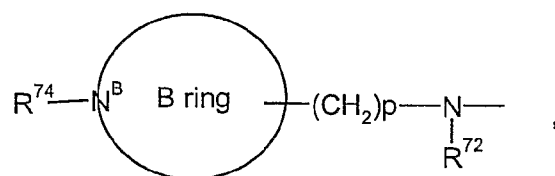
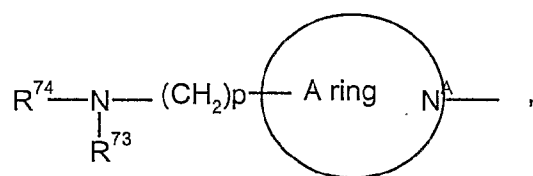
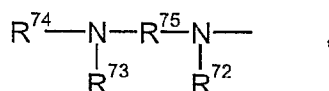
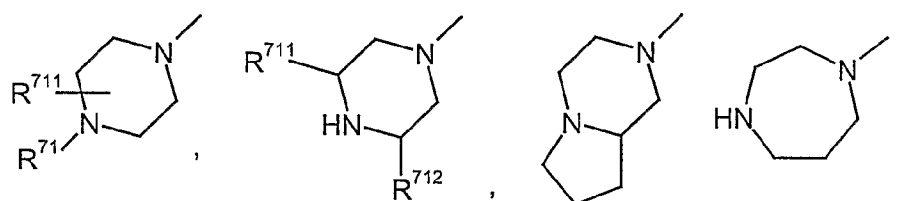
5

R^5 represents hydrogen, chloro, nitro, or cyano;

R^6 represents hydrogen;

10

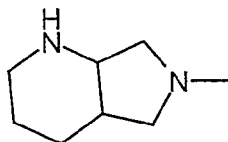
R^7 represents



15

- 216 -

or



wherein

R^{71} represents hydrogen, methyl, ethyl or isopropyl;

5

R^{711} represents hydrogen, methyl, or carboxy;

R^{712} represents hydrogen or methyl;

10

R^{72} is hydrogen, methyl, or ethyl;

R^{73} is hydrogen, methyl, or ethyl;

R^{74} is hydrogen, methyl, or ethyl; or

15

R^{73} and R^{74} may form, together with adjacent N atom, piperidino, or pyrrolidino,

R^{75} is phenyl;

20

p represents integer 0 or 1;

A ring represents piperidino, or pyrrolidino; and

25

B ring represents pyrrolidino.

13. The sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1, wherein said sulfonamide derivative is selected from the group consisting of:

- 5 1-{{2-(3,5-dimethylphenoxy)-5-nitrophenyl}sulfonyl}-4-ethylpiperazine,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}piperazine,
 1-{{2-(3,5-dimethylphenoxy)-5-nitrophenyl}sulfonyl}-4-isopropylpiperazine,
 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
 1-{{5-chloro-2-(3,5-dimethylphenoxy)phenyl}sulfonyl}-4-ethylpiperazine,
 10 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-4-(1-pyrrolidinyl)piperidine,
 4-(3,5-dichlorophenoxy)-3-{{4-(1-pyrrolidinyl)-1-piperidinyl}sulfonyl}benzo-
 nitrile,
 4-(3,5-dichlorophenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-N,N-diethyl-3-pyr-
 15 rolidinamine,
 (2S)-1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-2-(1-pyrrolidinyl-
 methyl)pyrrolidine,
 3-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylsulfonyl]-4-(3,5-
 dichlorophenoxy)benzonitrile,
 20 4-[(3,5-dichlorophenyl)sulfonyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 4-[(3,5-dichlorophenyl)sulfonyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 1-{{2-(3,5-dibromophenoxy)-5-nitrophenyl}sulfonyl}piperazine,
 1-{{2-(3,5-dichloro-2-fluorophenoxy)-5-nitrophenyl}sulfonyl}piperazine,
 1-{{5-cyano-2-(3,5-dichlorophenoxy)phenyl}sulfonyl}-2-piperazinecarboxylic
 25 acid,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-2-piperazinecarboxylic
 acid,
 1-{{2-(3,5-dimethylphenoxy)-5-nitrophenyl}sulfonyl}-1,4-diazepane,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-1,4-diazepane,
 30 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-3,5-dimethylpiperazine,
 3-(1,4-diazepan-1-ylsulfonyl)-4-(3,5-dichlorophenoxy) benzonitrile,

1'-{[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-1,3'-bipyrrolidine,
3-(1,3'-bipyrrolidin-1'-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile,
1-(2-[(3,5-dichlorophenyl)sulfanyl]-5-nitrophenyl)sulfonyl)-4-(1-pyr-
rolidinyl)piperidine,
5 4-(3,5-dichlorophenoxy)-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl-
sulfonyl)benzonitrile, and
3-(1,4-diazepan-1-ylsulfonyl)-4-[(3,5-dichlorophenyl)sulfanyl]benzonitrile.

14. A medicament comprising the sulfonamide derivative, its tautomeric or
10 stereoisomeric form, or a physiologically acceptable salt thereof as claimed in
claim 1 as an active ingredient.
15. A medicament as claimed in claim 14, further comprising one or more
pharmaceutically acceptable excipients.
- 15 16. A medicament as claimed in claim 14, wherein said sulfonamide derivative,
its tautomeric or stereoisomeric form, or a physiologically acceptable salt
thereof is a CCR3 antagonist.
- 20 17. An anti-inflammatory agent comprising the sulfonamide derivative, its
tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof
as claimed in claim 1 as an active ingredient.
18. An anti-inflammatory agent as claimed in claim 17;
- 25 wherein said agent is useful for treatment and prophylaxis of a disease
selected from the group consisting of asthma, rhinitis, and allergic diseases,
and autoimmune pathologies such as rheumatoid arthritis, Grave's disease,
and atherosclerosis.

19. An agent to treat or prevent a disease selected from the group consisting of HIV, lung granuloma, and Alzheimer's diseases ;
- 5 comprising the sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.
20. A method for treating or preventing a CCR3 related disorder or disease in a human or animal subject, comprising administering to said subject a
- 10 therapeutically effective amount of the sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1.
21. The method of claim 20, wherein said disorder or disease is a inflammatory or
- 15 immunoregulatory disorder or disease.
22. The method of claim 20, wherein said disorder or disease is selected from the group consisting of asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.
- 20 23. The method of claim 20, wherein said disorder or disease is selected from the group consisting of HIV, lung granuloma, and Alzheimer's diseases.
24. The method of claim 20, wherein said sulfonamide derivative is selected from
- 25 the group consisting of:
- 1 - {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl} -4-ethylpiperazine,
- 1 - {[2-(3,5-dichlorophenoxy)-5- nitrophenyl]sulfonyl} piperazine,
- 1 - {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl} -4-isopropylpiperazine,
- 30 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
- 1 - {[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl} -4-ethylpiperazine,

- 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-4-(1-pyrrolidinyl)-piperidine,
 4-(3,5-dichlorophenoxy)-3-{{4-(1-pyrrolidinyl)-1-piperidinyl}sulfonyl}-benzonitrile,
 5 4-(3,5-dichlorophenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-N,N-diethyl-3-pyrrolidinamine,
 (2S)-1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-2-(1-pyrrolidinylmethyl,)pyrrolidine,
 10 3-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylsulfonyl]-4-(3,5-dichlorophenoxy)benzonitrile,
 4-[(3,5-dichlorophenyl)sulfanyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 4-[(3,5-dichlorophenyl)sulfinyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 1-{{2-(3,5-dibromophenoxy)-5-nitrophenyl}sulfonyl} piperazine,
 15 1-{{2-(3,5-dichloro-2-fluorophenoxy)-5-nitrophenyl}sulfonyl} piperazine,
 1-{{5-cyano-2-(3,5-dichlorophenoxy)phenyl}sulfonyl}-2-piperazinecarboxylic acid,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-2-piperazinecarboxylic acid,
 20 1-{{2-(3,5-dimethylphenoxy)-5-nitrophenyl}sulfonyl}-1,4-diazepane,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-1,4-diazepane,
 1-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-3,5-dimethylpiperazine,
 3-(1,4-diazepan-1-ylsulfonyl)-4-(3,5-dichlorophenoxy) benzonitrile,
 25 1'-{{2-(3,5-dichlorophenoxy)-5-nitrophenyl}sulfonyl}-1,3'-bipyrrolidine,
 3-(1,3'-bipyrrolidin-1'-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile,
 1-{{2-[(3,5-dichlorophenyl)sulfanyl]-5-nitrophenyl}sulfonyl}-4-(1-pyrrolidinyl)piperidine,
 4-(3,5-dichlorophenoxy)-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-ylsulfonyl)benzonitrile, and
 30 3-(1,4-diazepan-1-ylsulfonyl)-4-[(3,5-dichlorophenyl)sulfanyl]benzonitrile.

25. The method of claim 20, wherein said sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is administered with one or more pharmaceutically acceptable excipients.
- 5
26. Use of the sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the preparation of a medicament
- 10
27. Use of the sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the preparation of a medicament for treating or preventing a CCR3 related disorder or disease.
- 15
28. The use of claim 27, wherein said disorder or disease is a inflammatory or immunoregulatory disorder or disease.
29. The use of claim 27, wherein said disorder or disease is selected from the group consisting of asthma, rhinitis, and allergic diseases, and autoimmune
- 20
- pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.
30. The use of claim 27, wherein said disorder or disease is selected from the group consisting of HIV, lung granuloma, and Alzheimer's diseases.
- 25
31. The use of claim 27, wherein said sulfonamide derivative is selected from the group consisting of:
- 1 - {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-4-ethylpiperazine,
- 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
- 30
- 1 - {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-4-isopropylpiperazine,
- 4-(3,5-dimethylphenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,

- 1 - {[5-chloro-2-(3,5-dimethylphenoxy)phenyl]sulfonyl}-4-ethylpiperazine,
 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-4-(1-pyrrolidinyl)-
 piperidine,
 4-(3,5-dichlorophenoxy)-3- {[4-(1-pyrrolidinyl)-1-piperidinyl]sulfonyl}-
 5 benzonitrile,
 4-(3,5-dichlorophenoxy)-3-(1-piperazinylsulfonyl)benzonitrile,
 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-N,N-diethyl-3-pyr-
 rolidinamine,
 (2S)-1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-2-(1-pyrrolidinyl-
 10 methyl,)pyrrolidine,
 3-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-ylsulfonyl]-4-(3,5-di-
 chlorophenoxy)benzonitrile,
 4-[(3,5-dichlorophenyl)sulfanyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 4-[(3,5-dichlorophenyl)sulfinyl]-3-(1-piperazinylsulfonyl) benzonitrile,
 15 1 - {[2-(3,5-dibromophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
 1 - {[2-(3,5-dichloro-2-fluorophenoxy)-5-nitrophenyl]sulfonyl}piperazine,
 1 - {[5-cyano-2-(3,5-dichlorophenoxy)phenyl]sulfonyl}-2-piperazinecarboxylic
 acid,
 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-2-piperazinecarboxylic
 20 acid,
 1 - {[2-(3,5-dimethylphenoxy)-5-nitrophenyl]sulfonyl}-1,4-diazepane,
 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-1,4-diazepane,
 1 - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-3,5-dimethylpiperazine,
 3-(1,4-diazepan-1-ylsulfonyl)-4-(3,5-dichlorophenoxy) benzonitrile,
 25 1' - {[2-(3,5-dichlorophenoxy)-5-nitrophenyl]sulfonyl}-1,3'-bipyrrolidine,
 3-(1,3'-bipyrrolidin-1'-ylsulfonyl)-4-(3,5-dichlorophenoxy)benzonitrile,
 1 - ({2-[(3,5-dichlorophenyl)sulfanyl]-5-nitrophenyl} sulfonyl)-4-(1-pyr-
 rolidinyl)piperidine,
 4-(3,5-dichlorophenoxy)-3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-
 30 ylsulfonyl)benzonitrile, and
 3-(1,4-diazepan-1-ylsulfonyl)-4-[(3,5-dichlorophenyl)sulfanyl]benzonitrile.

32. The use of claim 27, wherein said sulfonamide derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is formulated with one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09873

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/445 A61K31/496 A61P11/06 A61P37/00 A61P29/00
 C07D295/22 C07D471/04 C07D211/58 C07D243/06 C07D211/28
 C07C311/18 C07D211/96 C07D307/14 C07D207/14 C07D213/71

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 819 639 A (DELARGE J ET AL) 25 June 1974 (1974-06-25) examples 6,16 ---	1,14,15, 26
X	WO 01 32604 A (GLEN ROBERT ;SELWOOD DAVID (GB); UNIV LONDON (GB); WISHART GRANT () 10 May 2001 (2001-05-10) page 72, line 20 ---	1,14,15, 26
X	WO 00 42003 A (BARRETT STEPHEN DOUGLAS ;WARNER LAMBERT CO (US); TECLE HAILE (US);) 20 July 2000 (2000-07-20) page 9, line 4 - line 5 ---	1,14,15, 26
X	US 2 275 354 A (ALEXANDER PHILLIPS MONTAGUE ET AL) 3 March 1942 (1942-03-03) example 16 --- -/--	1,14,15, 26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

7 November 2002

Date of mailing of the international search report

02/12/2002

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAARI ET AL.: "Synthesis and evaluation of some nitrobenzenesulfonamides containing nitroisopropyl and (ureidooxy)methyl groups as novel hypoxic cell selective cytotoxic agents." J. MED. CHEM., vol. 34, no. 10, 1991, pages 3132-3138, XP000605240 Compound 3	1
X	----- DATABASE CHEMCATS 'Online! Chemical abstracts service, Columbus, Ohio, US; XP002219853 Order Numbers: 7J-012, 7J-005, 7J-004 & "Ambinter Screening Collection" 31 May 2001 (2001-05-31), AMBINTER, PARIS F-75016, FRANCE	1
X	----- DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 491793 XP002219854 abstract & MASTRUKOVA ET AL: TETRAHEDRON, vol. 19, 1963, pages 357-368,	1
X	----- DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 590986 XP002219855 abstract & DELARGE: ANN. PHARM. FR., vol. 31, 1973, pages 467-469,	1
A	----- "Chemokine CCR3 antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 10, no. 8, 2000, pages 1455-1459, XP002219852 the whole document	1-32
A	----- WO 99 55324 A (SMITHKLINE BEECHAM CORP ;DHANAK DASHYANT (US)) 4 November 1999 (1999-11-04) the whole document	1-32

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5 (part)

Present claims 1-5 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the complete search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) wherein the sulfonamide group is ortho to the -Y-X group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/09873

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-5 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/09873

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			JP 2002512957 T	08-05-2002
			WO 9955324 A1	04-11-1999
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